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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **High-quality anticoagulation management is required to keep these narrow therapeutic index medications as effective and safe as possible. This article focuses on the common important management questions for which, at a minimum, low-quality published evidence is available to guide best practices.**

Methods: **The methods of this guideline follow those described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.**

Results: **Most practical clinical questions regarding the management of anticoagulation, both oral and parenteral, have not been adequately addressed by randomized trials. We found sufficient evidence for summaries of recommendations for 23 questions, of which only two are strong rather than weak recommendations. Strong recommendations include targeting an international normalized ratio of 2.0 to 3.0 for patients on vitamin K antagonist therapy (Grade 1B) and not routinely using pharmacogenetic testing for guiding doses of vitamin K antagonist (Grade 1B). Weak recommendations deal with such issues as loading doses, initiation overlap, monitoring frequency, vitamin K supplementation, patient self-management, weight and renal function adjustment of doses, dosing decision support, drug interactions to avoid, and prevention and management of bleeding complications. We also address anticoagulation management services and intensive patient education.**

Conclusions: **We offer guidance for many common anticoagulation-related management problems. Most anticoagulation management questions have not been adequately studied.**

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Abbreviations: AMS = anticoagulation management service; aPTT = activated partial thromboplastin time; COX = cyclooxygenase; FFP = fresh frozen plasma; HR = hazard ratio; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NSAID = nonsteroidal antiinflammatory drug; PCC = prothrombin complex concentrate; PE = pulmonary embolism; POC = point-of-care; PSM = patient self-management; PST = patient self-testing; RCT = randomized controlled trial; RR = risk ratio; SC = subcutaneous; TTR = time in therapeutic range; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating vitamin K antagonist (VKA) therapy with warfarin 10 mg

daily for the first 2 days followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose (Grade 2C).

2.2. For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).

2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of LMWH or UFH therapy rather than waiting for several days to start (Grade 2C).

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B).

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C).

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C).

3.4. For patients taking VKAs, we suggest against routine use of vitamin K supplementation (Grade 2C).

3.5. (Best Practices Statement) We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.

3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest patient self-management (PSM) rather than usual outpatient INR monitoring (Grade 2B). **For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.**

3.7. For dosing decisions during maintenance VKA therapy, we suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C).

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.

3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2-selective NSAIDs, and certain antibiotics (see Table 8) (Grade 2C).

For patients taking VKAs, we suggest avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C).

4.1. For patients treated with VKAs, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR < 2) or higher (INR 3.0-5.0) range (Grade 1B).

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B).

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5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C)**.**

6.1. For patients starting IV unfractionated heparin (UFH), we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or use of a fixed dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C)**.**

6.2. For outpatients with VTE treated with subcutaneous (SC) UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring (Grade 2C)**.**

7.1. For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min), we suggest a reduction of the dose rather than using standard doses (Grade 2C)**.**

8.1. For patients with VTE and body weight over 100 kg, we suggest that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily SC (Grade 2C)**.**

9.1.

(a) For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B)**.**

(b) For patients taking VKAs with INRs > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered (Grade 2C)**.**

9.2. For patients initiating VKA therapy, we suggest against the routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy (Grade 2C)**.**

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate (PCC) rather than with plasma. (Grade 2C)**.**

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C)**.**

This article deals with the evidence regarding managing anticoagulant therapy, that is, oral vitamin K antagonists (VKAs), heparins, and fondaparinux. Separate articles address the pharmacology of these drugs.[1] The questions that we address reflect those commonly posed in clinical practice.

1.0 Methods

The methods for the development of this article's recommendations follow those developed for the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.[2] Although we aimed to summarize and use randomized controlled trial (RCT) evidence to inform recommendations for clinicians, we found only lower-quality evidence to address most of our questions. At the onset of our review process, our panel decided to limit the recommendations to questions in which evidence met a minimum threshold for quality: at least one comparative study with ≥ 50 patients per group with contemporaneous or historical controls reporting on patient-important outcomes or closely related surrogates. Despite this low threshold, evidence was unavailable for several important clinical management questions. When randomized trials were available, confidence in estimates often decreased because of indirectness (surrogate outcomes) and imprecision (wide CIs).

This article does not address anticoagulation management issues specific to pregnancy or to children. Issues believed to be specific to a particular diagnosis, such as VTE or atrial fibrillation, are dealt with in those specific articles of this supplement. Table 1 presents the questions for which we found evidence that met our quality threshold, including the relevant populations, interventions, comparators, and outcomes.

2.0 VKA—Initiation of Therapy

2.1 Initial Dose Selection—Loading Dose

Loading doses of VKA may be worth considering where rapid attainment of therapeutic international normalized ratio (INR) is required and considered safe, primarily for patients with VTE. Predictable and timely achievement of therapeutic INRs without increased risk of bleeding or recurrent thromboembolic events avoids the inconvenience and pain of prolonged administration of subcutaneous (SC) low-molecular-weight heparin (LMWH) and facilitates early patient discharge and eligibility for outpatient dosing nomograms. Two large case series[5,6] involving a total of 1,054 outpatients suggest that a nomogram specifying a 10-mg loading dose is safe, with a recurrent VTE rate of 1.9% and a major bleeding rate of 1.0% at 3 months follow-up.[5] However, pooling across both studies suggests that only 49.3% of participants followed the nomogram completely.

Table 2 and Table S1 (tables that contain an "S" before the number denote supplementary tables

Table 1—*Structured Clinical Questions*

Section	Informal Question	PICO: Population	PICO: Intervention	PICO: Comparator	PICO: Outcome	Comment
2.0 VKAs—initiation of therapy						
2.1. Loading doses of VKA	Is a loading dose of VKA superior to no loading dose?	Patients taking VKA	Loading dose	No loading dose	Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR	
2.2. Dose by Pharmacogenetics	Should the initial dose of VKA be based on pharmacogenetic testing?	Patients taking VKA	Analysis of CYP2C9, VKORC1, and other polymorphisms	No pharmacogenetic testing	Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR	
2.3. Initiation overlap	Should VKA be started simultaneously with heparin rather than delayed a few days?	Patients treated for acute thromboembolism (or other high-risk situation requiring long-term VKA)	Simultaneous start	Initial heparin followed by overlap with VKA	Hemorrhage, thromboembolic events, time to therapeutic range, rates of supratherapeutic or subtherapeutic INR, resource utilization (hospital stay)	
3.0 VKAs—maintenance treatment						
3.1. INR monitoring frequency	How frequently should treatment be monitored initially and once dose and INR have been stable for months?	Patients taking VKA	Higher frequency	Lower frequency	Hemorrhage, thromboembolic events, time to therapeutic range	
3.2. Single out-of-range INR—dose adjustment	Should the VKA dose change for a single deviating INR in otherwise stable patients?	Patients taking VKA	Dose adjustment	Continue as usual	Hemorrhage, thromboembolic events, time in therapeutic range	
3.3. Bridging for subtherapeutic INR	Does bridging anticoagulant therapy improve outcomes for low INR?	Patients taking VKA with subtherapeutic INR	Dose management and overlapping with heparin	Only dose management	Hemorrhage, thromboembolic events, time in therapeutic range	
3.4. Vitamin K supplementation	Can outcomes be improved with low-dose vitamin K supplementation or dietary manipulation?	Patients taking VKA with variability of INR	Cotherapy with small-dose vitamin K or with dietary modification	No vitamin K	Hemorrhage, thromboembolic events, time in therapeutic range	
3.5. Dose management services	Dose management services: does a specialized AMS improve outcomes?	Patients taking VKA	AMS care	Usual care (primary care or regular hospital physicians)	Hemorrhage, thromboembolic events, time in therapeutic range, resource utilization	
3.6. Patient self-testing and self-monitoring	Does self-monitoring of anticoagulation improve outcomes	Patients taking VKA	Use of point-of-care monitor at home to measure INR and to adjust VKA dose	Usual care or AMS care	Hemorrhage, thromboembolic events, time in therapeutic range, resource utilization	

(Continued)

Table 1—*Continued*

Section	Informal Question	PICO: Population	PICO: Intervention	PICO: Comparator	PICO: Outcome	Comment
3.7. Dosing decision support	Does dosing decision support improve outcomes	Patients taking VKA	Computer software, manual algorithms	Usual care	Hemorrhage, thromboembolic events, time in therapeutic range, resource utilization	
3.8. Drug interactions to avoid	What anticoagulant drug or food interactions are important enough to avoid the interacting drug while patients take anticoagulants	Patients taking anticoagulants	Patients starting or stopping potentially interacting drugs	Patients not taking potentially interacting drugs	Hemorrhage, thromboembolic events, time in therapeutic range	Limited to randomized trials of clinical outcomes or large observational studies
4.0 VKAs—monitoring						
4.1. Optimal INR range	What is the optimal INR range for best clinical outcomes?	Patients taking VKA	Optimal INR range	Wider INR range	Hemorrhage, thromboembolic events	
4.2. Optimal INR range for high-risk groups	Should high-risk groups (such as APS, cancer) be treated more intensively?	Patients with APS (or other high-risk feature) and taking VKA	More intensive INR therapeutic range or alternative assay	Standard INR therapeutic range	Hemorrhage, thromboembolic events, time in therapeutic range	
5.0 VKAs—discontinuing therapy						
5.1 Tapering vs abrupt discontinuation	How should VKA be discontinued?	Patients discontinuing VKA	Tapered discontinuation	Abrupt discontinuation	Hemorrhage, thromboembolic events, time to normal anticoagulation status	
6.0 Parenteral anticoagulants—UFH						
6.1. UFH—dose adjustment by weight	Should the initial bolus dose or maintenance dose be weight adjusted?	Patients treated with IV UFH	Weight-adjusted dose	Fixed dose	Hemorrhage, thromboembolic events, time in therapeutic range	
6.2. SC UFH dose adjustment and monitoring	Should doses of SC UFH be adjusted for weight and monitored by aPTT?	Patients treated with SC UFH	Weight-adjusted dose with and without aPTT monitoring	Fixed dose with or without aPTT monitoring	Hemorrhage, thromboembolic events, time in therapeutic range	
7.0 Parenteral anticoagulants—LMWH						
7.1. LMWH—dose modification by renal function	Should doses be modified for renal function?	Patients with mild to moderate renal failure treated with LMWH	Dose adjustment according to renal function	Dose adjustment only by body weight or no dose adjustment	Hemorrhage, thromboembolic events	
7.2. LMWH—dose Frequency	Can doses be administered daily instead of twice daily?	Patients treated with LMWH	Doses administered daily	Doses administered bid	Hemorrhage, thromboembolic events	Moved to Kearon et al[3] in this supplement
7.3. LMWH dose modification by weight for prophylaxis	Should the dose be weight adjusted?	Obese or significantly underweight patients receiving prophylaxis with LMWH	Dose adjustment according to body weight	Standard dose	Hemorrhage, thromboembolic events	Gould et al[4] in this supplement

(Continued)

Table 1—*Continued*

Section	Informal Question	PICO: Population	Intervention	Comparator	Outcome	Comment
8.0 Parenteral anticoagulants—fondaparinux						
8.1. Fondaparinux dose management	Should the dose be weight adjusted?	Obese or significantly underweight patients receiving fondaparinux	Dose adjustment according to body weight	Standard dose	Hemorrhage, thromboembolic events	
9.0 Prevention and management of anticoagulant complications						
9.1. Vitamin K for high INR without bleeding	Does vitamin K improve outcomes for high INRs without bleeding?	Patients taking VKA with high INR (> 4.5) without bleeding	KA dose management plus use of vitamin K	Only dose management (= holding the VKA until therapeutic)	Hemorrhage, thromboembolic events, time to therapeutic range, rates of overcorrection of INR	
9.2. Predicting anticoagulant-associated bleeding	Does a bleeding clinical prediction rule improve outcomes? Which prediction rule should be used?	Patients taking anticoagulant therapy or considering therapy	Use of a bleeding clinical prediction rule to guide therapy (dose and whether to give)	No clinical prediction rule or alternate prediction rule	Hemorrhage, thromboembolic events, choice of therapy	
9.3. Treatment of anticoagulant-related bleeding	What is the most effective and safe urgent treatment of anticoagulant-related bleeding?	Patients actively bleeding from excessive anticoagulation who need to have the bleeding stopped urgently	Vitamin K, FFP, PCC, recombinant factor VIIa	One of the other treatments or vitamin K alone	Time to resolution of bleeding, bleeding complications, thromboembolism rates, resource utilization	
9.4. Investigating anticoagulant-associated bleeding	When is it appropriate to investigate anticoagulant-associated bleeding?	Patients taking VKAs with therapeutic INRs and major bleeding episodes	Patients who bleed	Patients who do not bleed	Incidence of malignancy, ulcer disease, other serious or treatable outcome	
10.0 Other						
10.1. Intensive patient education	Does additional structured patient education improve outcomes related to anticoagulation?	Patients who are to take or are taking VKAs or parenteral anticoagulants	Patient education on benefits, harms, and use of anticoagulants	Usual care	Hemorrhage, thromboembolic events, time in therapeutic range, compliance	

AMS = anticoagulant management service; APS = antiphospholipid syndrome; aPTT = activated partial thromboplastin time; LMWH = low-molecular-weight heparin; FFP = fresh frozen plasma; INR = international normalized ratio; PCC = prothrombin complex concentrate; PICO = population, intervention, comparator, and outcome; UFH = unfractionated heparin; VKA = vitamin K antagonist; VKORC1 = vitamin K epoxide reductase complex 1.

Table 2—*[Section 2.1] Warfarin 10 mg Loading Dose Nomogram Compared With Warfarin 5 mg Loading Dose Nomogram for Warfarin Initiation*[7,8,10,11]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Warfarin 5 mg Loading Dose Nomogram	Anticipated Absolute Effects: Risk Difference With Warfarin 10 mg Loading Dose Nomogram (95% CI)
Bleeding events	420 (3 studies[a-c]), 5-90 d[d]	Very low[e-g] due to indirectness, imprecision	OR 1.90 (0.17-21.1)	5 per 1,000	0 more per 1,000 (from 10 fewer to 20 more)[h]
Recurrent VTE	420 (3 studies[a-c])	Very low[e-g] due to indirectness, imprecision	Not estimable	0 per 1,000	10 more per 1,000 (from 30 more to 0 more)[i]

GRADE = Grades of Recommendations, Assessment, Development, and Evaluation. See Table 1 legend for expansion of other abbreviation.
[a]All pooled studies included only patients with acute VTE. Studies from which data could be pooled are Kovacs et al,[9] Quiroz et al,[10] and Schulman et al.[11]
[b]Minimal loss to follow-up; adherence to intention-to-treat principle in two of three studies; follow-up period short but adequate for this outcome; any lack of blinding should not impact objective outcome (laboratory value, INR); adequate allocation concealment; sample size calculations reported for two of three studies.
[c]Results based on only three studies; one study shows no difference; one shows statistically significant reduction in time to therapeutic INR; and one had two parts to it, where one showed statistically significant reduction and the other did not.
[d]Mean follow-up period of 5 d for patients in the loading dose warfarin group from Schulman et al[11] (this was the shortest period, only mean is available).
[e]Data collectors unblinded.
[f]Indirect given application aimed at outpatients with VTE; follow-up period is very short in two of three studies (5 d-2 wk).
[g]No studies were powered to detect differences in bleeding events between groups. Number of events is too sparse to draw any conclusions.
[h]Very small number of events; risk difference calculated.
[i]OR not estimable; absolute risk difference calculated.

not contained in the body of the article and available instead in an online data supplement; see the "Acknowledgments" for more information) summarizes our confidence in effect estimates and main findings from a meta-analysis of five RCTs of loading dose vs no loading dose of warfarin.[7-11] The table shows that clinical outcomes, where documented, were similar between the groups. The studies typically measured time to therapeutic range of anticoagulation as the primary outcome and the patients were mainly those starting treatment (not prophylaxis) for VTE. Many of those treated as inpatients at the time of the study would, in current practice, be treated as outpatients.

Two studies by a single group[7,8] compared a 10-mg loading dose to 5 mg daily for the first 2 days. Both included primarily inpatients, and one did not report recurrent VTE.[8] The concentrations of protein C and factor VII, but not those of factor II or X, decreased faster in the 10-mg group than in the 5-mg group[8]; an increased risk of recurrent thromboembolism, however, has not been demonstrated in any of the studies presumably because initiation overlaps with heparin or LMWH. Quiroz et al[10] compared 5 vs 10 mg initial warfarin dosing in 50 inpatients and reported no difference in median time to two consecutive therapeutic INRs. This study had only a 2-week follow-up and excluded 322 of the 372 patients screened. Another study compared loading dose vs standard warfarin initiation for patients with VTE and showed a shorter time to a therapeutic INR (3.3 vs 4.3 days).[11] Finally, Kovacs et al[9] found that the use of a 10- vs 5-mg initiation nomogram with 210 outpatients resulted in shorter mean time to therapeutic INR of 4.2 vs 5.6 days. The proportion therapeutic by day 5 was also significantly better at 86% vs 45% in the 10- vs 5-mg group, respectively. All studies followed the initiation period with INR-based dose adjustment.

Recommendation

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on INR measurements rather than starting with the estimated maintenance dose (Grade 2C)**.**

2.2 Initial Dose Selection and Pharmacogenetic Testing

Selection of the initial and maintenance doses of VKA therapy usually has been based on subjective estimates of patient age, size, nutritional status, and organ function. In section 2.1, we suggest a standard short loading dose for outpatients. Theoretically, individual patient pharmacogenetic testing of CYP2C9 (cytochrome P450 2C9), which is involved with VKA metabolism and VKORC1 (vitamin K epoxide reductase complex 1, the VKA target), might improve VKA therapy through more-accurate dose selection. There are four RCTs of pharmacogenetic testing-based dosing vs standard dosing; all addressed warfarin initiation.[12-15] The studies included patients with

artificial heart valves, atrial fibrillation, or acute VTE. All studies were small (total n = 544). None showed any difference in thrombotic events, major bleeding, or survival (Table S2).

Hillman et al[12] conducted a pilot study of 38 patients. Caraco et al[13] randomized 283 patients but excluded 92 for reasons such as failure to follow warfarin dosing instructions. Huang et al[15] included 121 valve inpatients and showed improvement in time to therapeutic range; the control group, however, used a substandard 2.5-mg daily regimen. Anderson et al,[14] who had the highest methodologic quality, studied inpatients in which the control group experienced close INR monitoring following a loading-dose strategy. The investigators found no difference in time in therapeutic range or time to therapeutic range. A systematic review also concluded that there is a lack of evidence to support using pharmacogenetic testing to guide VKA dosing.[16]

Several recent economic evaluations have assessed the cost-effectiveness of pharmacogenetic testing to guide VKA (warfarin) initiation.[17-19] The results of these studies estimated the incremental cost at ~$50,000 to $170,000 per quality-adjusted life year gained, but in sensitivity analyses, the incremental cost-effectiveness ratios were as high as $200,000 to $300,000 per quality-adjusted life year and included scenarios in which pharmacogenetic testing led to poorer patient outcomes. These results would be judged as not cost-effective by most drug policy experts.

Recommendation

2.2. For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B)**.**

2.3 Initiation Overlap for Heparin and VKA

Historically, clinicians administered IV unfractionated heparin (UFH) to inpatients for 5 to 7 days with subsequent initiation of a VKA, leading to a total duration of IV UFH of 10 to 14 days. More recently, VKA therapy has been initiated on the first or second day of heparin therapy, leading to shorter durations of heparin and earlier discharge from the hospital.

Table 3 (and Table S3) summarizes the evidence from a meta-analysis of 807 patients in four RCTs

Table 3—*[Section 2.3] VKA Started Early vs Late With Heparin in Patients With Acute Thromboembolism*

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Late	Anticipated Absolute Effects: Risk Difference With VKA Started Early (95% CI)
Death	807 (4 studies), 3-6 mo	Low[a-c] due to inconsistency and imprecision	RR 1.28 (0.43-3.85)	58 per 1,000	16 more per 1,000 (from 33 fewer to 166 more)
Recurrent thromboembolism DVT: venography, Doppler ultrasonography or impedance plethysmography. PE: lung scanning Left ventricle thrombus: 2-dimensional transthoracic echocardiography	807 (4 studies), 3-6 mo	Low[c,d] due to risk of bias and imprecision	RR 0.92 (0.46-1.82)	41 per 1,000	3 fewer per 1,000 (from 22 fewer to 33 more)
Major bleeding-required blood transfusion, bleeding in body cavity, bleeding that required anticoagulation withdrawal or intracranial or retroperitoneal, or bleeding that led to a hemoglobin level decrease of ≥ 2 g/dL or to death	807 (4 studies), 0.5-6 mo	Low[c,d] due to risk of bias and imprecision	RR 1.22 (0.58-2.56)	33 per 1,000	7 more per 1,000 (from 14 fewer to 51 more)
Hospital utilization	536 (3 studies)	High		The mean hospital utilization in the control groups was 14 d	The mean hospital utilization in the intervention groups was 4.07 lower (4.76 to 3.37 lower)

PE = pulmonary embolism; RR = risk ratio. See Table 2 legend for expansion of other abbreviation.
[a]For three out of four studies, concealment of allocation was unclear. Lack of blinding of health-care professionals in some studies.
[b]The value for I2 test for death was 55%, and therefore, it was rated down for inconsistency.
[c]The 95% confidence intervals around the absolute risk values were very wide for this outcome.
[d]Potential limitations in design for this outcome: allocation sequence concealment was not reported in three out of four studies; health-care professionals blinded in only one study (Hull et al[20]) (outcome assessors were blinded in three of four studies).

addressing this issue (F. Qayyum, unpublished data, 2011). These trials compared early start (day 1 or 2 of heparin) vs late start (days 3-10 of heparin) for the VKA therapy together with UFH or LMWH therapy. Two studies[20,21] enrolled patients with DVT only, one enrolled patients with DVT or pulmonary embolism (PE),[22] and the fourth included patients with left ventricular mural thrombosis.[22] There were no differences between early vs late initiation of VKA for the outcomes of recurrent VTE, major bleeding, or death. Patients assigned to early initiation of VKA spent a mean of 4 fewer days in the hospital than patients assigned to late initiation of VKA. No studies have assessed early vs late initiation of VKA therapy in the outpatient setting, but we consider the results of the meta-analysis to be applicable to outpatients.

Recommendation

2.3. For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of LMWH or UFH therapy rather than waiting for several days to start (Grade 2C)**.**

3.0 Maintenance Treatment With VKAs

3.1 Monitoring Frequency for VKAs

The frequency of long-term INR monitoring is influenced by patient compliance, changes in health status, the addition or discontinuation of interacting medications, changes in diet, the quality of dose-adjustment decisions, and whether the patient has demonstrated stable INRs.[23-25] We define stable INRs as at least 3 months of consistent results with no need to adjust VKA dosing.[26] Recall intervals for various clinical situations have not been extensively studied; rather, they evolved from routine clinical practice and expert opinion and differ substantially from one country to another.[27] For example, in North America, stable patients usually are tested every 4 weeks,[24] whereas in the United Kingdom, INR recall intervals of up to 90 days are routine.[28] This discussion does not apply to patients engaging in INR self-testing using portable finger-stick monitors in whom only weekly INR recall intervals have been adequately evaluated.

For patients receiving traditional laboratory-based INR monitoring, retrospective studies have found increasing INR recall intervals associated with both increased[29] and decreased[26,30] time in therapeutic range (TTR). Other observational studies have suggested that for patients who demonstrate a consistent pattern of stable therapeutic INRs, allowing INR recall intervals of up to 8 weeks would not result in increased risk for bleeding or thromboembolism.[31-33]

Three RCTs have evaluated the effectiveness of INR recall intervals exceeding the traditional North American standard of 4 weeks.[23,34,35] One study compared 6- to 4-week recall intervals,[34] whereas another evaluated a flexible approach that allowed recall intervals of up to 12 weeks based on several factors, including the number of prior INRs, longitudinal INR variability, and the risk of adverse events expressed as a function of the INR.[23] The third study compared 4- to 12-week recall intervals using a blinded design.[35] None of the studies found a difference in rates of thromboembolism, bleeding, or INR control (Table 4, Table S4). The appropriate length of the recall interval depends on the duration of prior stability and foreseeable future changes in medications or disorders that affect the INR. Whatever maintenance dose interval is chosen, when adjustments to the VKA dose are required, a cycle of more-frequent INR monitoring should be completed until a consistent pattern of stable therapeutic INRs can be reestablished.[36]

Recommendation

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B)**.**

3.2 Management of the Single Out-of-Range INR

A common dilemma encountered in clinical management of patients taking VKAs is what to do with an INR slightly outside the therapeutic range when

Table 4—*[Section 3.1] Prolonged INR Recall Intervals Compared With 4-Week Recall Intervals for Patients With a Stable INR*[23,34,35]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]: Risk With 4-wk Recall Intervals	Anticipated Absolute Effects[a]: Risk Difference With Prolonged INR Recall Intervals (95% CI)
Thromboembolism variously defined	994 (3 studies), 313 patient-y	Moderate[b] due to imprecision	OR 1.05 (0.28-3.97)	12 per 1,000	1 more per 1,000 (from 8 fewer to 33 more)
Major bleeding variously defined	994 (3 studies), 313 patient-y	Moderate[b] due to imprecision	RR 1.12 (0.57-2.23)	33 per 1,000	4 more per 1,000 (from 14 fewer to 41 more)

See Table1-3 legends for expansion of abbreviations.
[a]Time frame in months.
[b]Wide CIs around the estimate of effect.

INRs were previously in the therapeutic range.[25] The question is whether the dose should be adjusted or left unchanged until the next INR is obtained.

This issue has been evaluated in two studies. An open-label RCT compared a one-time dose increase or hold vs continuing as is when the INR was slightly below or above the therapeutic range.[37] Randomized patients had been taking a stable warfarin dose for at least 3 months, the out-of-range INR was between 1.5 and 4.4, and the target ranges were 2.0 to 3.0 or 2.5 to 3.5. Reduced or boosted doses were usually 50% lower or higher, respectively, than the regularly scheduled dose. Results were similar at follow-up ~2 weeks later, with 44% outside the therapeutic range among patients randomized to a one-time dose change compared with 40% of those randomized to no dose change (OR, 1.17; 95% CI, 0.59-2.30; $P = .75$).

The other study evaluated the safety of not changing the usual warfarin maintenance dose in response to isolated, asymptomatic INRs of 3.2 to 3.4 in patients who had been taking warfarin for at least 30 days and had a targeted INR range of 2.0 to 3.0.[38] This was an observational study nested within an RCT evaluating anticoagulation management services (AMS) vs primary care management. The response to an isolated INR between 3.2 and 3.4 was to continue the same dose 78% of the time in AMS vs 47% in primary care. The proportion of patients with a therapeutic follow-up INR was not significantly different between the two groups (AMS, 63%; control, 54%). No major bleeding or thromboembolic events were observed during the 14 to 30 days follow-up in either of these studies.

The evidence from both studies suffers from relatively small sample sizes; lack of blinding; and in the second study, lack of randomization and a lack of uniformity in INR management between groups. Both studies were consistent with a dosing model developed from an observational study of 3,961 patients that suggested that warfarin doses did not need to be changed for INRs between 1.7 and 3.3.[25] It is reasonable to follow up with an INR after 1 to 2 weeks to exclude a progressive deviation from the therapeutic range.[36,37]

Recommendation

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤ 0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C)**.**

3.3 Bridging for Low INRs

When the INR becomes subtherapeutic, there may be an increased risk of thrombosis. A 2008 retrospective study of 2,597 adult patients receiving warfarin mainly for atrial fibrillation or VTE matched 1,080 patients in the low-INR cohort with 1,517 patients in the therapeutic-INR cohort based on index INR date, indication for warfarin, and age.[39] All patients in the low-INR cohort had a subtherapeutic INR following two therapeutic INR measurements. There was no significant difference in thromboembolic events between the two groups, including the small number (99) of patients with artificial heart valves.

A second retrospective study addressed the same scenario in 294 patients with mechanical heart valves.[40] Bridging with LMWH was prescribed in 14 cases. The incidence of thromboembolic events was found to be 0.3% (95% CI, 0%-1.9%) for all patients included in the study and 0.4% (95% CI, 0%-2.0%) for all patients who did not receive bridging therapy. Both studies are limited by the observational study design and its potential for confounding. Unfortunately, this evidence only addresses the single low INR, not several consecutive low INRs.

Recommendation

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C)**.**

3.4 Vitamin K Supplementation

A low TTR as well as highly variable INR results are independent predictors of bleeding and thromboembolic complications during VKA therapy. One observational study using food diaries to quantify daily vitamin K intake showed that patients in the highest tertile of vitamin K intake had the most stable INR control over time, suggesting the possibility that daily vitamin K supplementation might improve anticoagulation control.[41]

Three randomized, placebo-controlled trials using pharmaceutically prepared vitamin K have addressed this issue.[42-44] There are important differences among these RCTs, including the daily dose of vitamin K studied (100 μg,[42,44] 150 μg,[43,44] or 200 μg[44]), the study participants (general anticoagulation clinic patients[42,44] or patients with unstable INR control[43]), the width of targeted INR range (1.5[42,44] or 1.0), and type of VKA (phenprocoumon or warfarin). Table 5 (and Table S5) shows the quality of evidence and main findings of our meta-analysis of the three RCTs. The absolute difference in TTR was a modest 3.54% (95% CI, 1.13%-5.96%). No difference in major bleeding or thromboembolic complications was seen.

The TTR observed in the control arms of these vitamin K RCTs indicates that studied patients had relatively stable INRs (TTR range, 78.0%-85.5%). It

Table 5—*[Section 3.4] Low-Dose Vitamin K Supplementation Compared With Placebo for Patients Taking VKAs To Stabilize INR*[42-44]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]	
				Risk With Placebo	Risk Difference With Low-Dose Vitamin K Supplementation (95% CI)
Thromboembolism	626 (3 studies), 6-12 mo	Very low[b-e] due to inconsistency, imprecision	RR 1.65 (0.08-34.03)	0 per 1,000	Not estimable[f]
Major bleeding	626 (3 studies), 6-12 mo	Very low[b-e] due to inconsistency, imprecision	RR 2.61 (0.34-20.28)	0 per 1,000	Not estimable[f]

See Table 1-3 legends for expansion of abbreviations.
[a]Time frame in months.
[b]Allocation concealment not reported; uncertain whether outcome adjudicators were blinded.
[c]Definition of thromboembolism and major bleeding different in each study.
[d]Studies not powered to detect bleeding or thromboembolic events; total number of events is extremely low.
[e]Unable to rule out publication bias because not enough studies exist to populate a funnel plot.
[f]Total of two thromboembolic and three major bleeding events in low-dose vitamin K groups.

would be of greater interest to evaluate the effect of daily vitamin K supplementation in a population with unstable INRs that are not due to other correctable factors. In summary, current evidence does not support supplementation with vitamin K to increase TTR or to improve clinical outcomes.

Recommendation

3.4. For patients taking VKAs, we suggest against routine use of vitamin K supplementation (Grade 2C)**.**

3.5 Anticoagulation Management Services for VKAs

In response to the recognized difficulty in coordinating oral anticoagulation therapy, AMS have evolved in both inpatient and outpatient settings. For the purposes of this review, an AMS was defined as having a designated, trained staff member responsible for patient INR monitoring and follow-up, the use of a standardized local procedure for VKA management (eg, dosing nomogram), and the management of regular INR testing. Further, usual care was defined as regular medical care that generally was provided by the patient's personal physician in the absence of an AMS.

Four prospective RCTs comparing usual care with the care of an AMS failed to show a significant difference in major bleeding, thromboembolism, or anticoagulation therapy-related mortality.[45-48] None of these RCTs were blinded, only two studies clearly specified an intention-to-treat analysis,[46-48] one study allowed patients to switch between treatment arms,[45] and all patients in two studies were stabilized in an AMS prior to randomization.[45,48]

In contrast, the results of many low-quality observational studies have reported higher TTR and better outcomes in patients when anticoagulant therapy is managed by an AMS compared with usual care.[49-65] The absolute difference in TTR between AMS and community practices in a systematic review was 8.3% (95% CI, 4.4%-12.1%), favoring AMS.[66]

Given the conflicting results between randomized and nonrandomized studies and the lack of economic analysis or compelling patient preference data, the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines committee decided to make the following best practice statement on this question:

3.5. We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions.

3.6 Patient Self-Testing and Self-Management

Patients using long-term oral anticoagulation therapy usually are monitored by going to a hospital or laboratory to provide blood by venipuncture for INR testing. Point-of-care (POC) devices allow INR testing to be performed by patients in their homes with a drop of blood from the finger. This is defined as patient self-testing (PST). If the patients who perform their own INR testing also adjust their anticoagulant dose, this is called patient self-management (PSM).[67] Several systematic reviews have evaluated RCTs of PST/PSM to determine whether these approaches to oral anticoagulation therapy result in better clinical outcomes than traditional laboratory-based INR monitoring.[67-71] A recent individual patient meta-analysis clarified several aspects; our recommendations are based primarily on this more-detailed analysis.[72]

Pooled analyses show a significant reduction in the rate of thromboembolic complications with PST/PSM but not in the rate of major bleeding or overall mortality compared with usual laboratory-based INR

Table 6—*[Section 3.6] Patient Self-Testing/Self-Monitoring Compared With Usual Laboratory-Based Monitoring for VKA Therapy Management*[72]

				Anticipated Absolute Effects[a]	
Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Risk With Usual Laboratory-Based Monitoring	Risk Difference With Patient Self-Testing/Patient Self-Monitoring (95% CI)
Thromboembolism various methods[b]	6,417 (11 studies), 3-36 mo	Low[c,d] due to risk of bias, inconsistency	OR 0.51 (0.31-0.85)	48 per 1,000	23 fewer per 1,000 (from 7 fewer to 33 fewer)
Major bleeding various definitions[b]	6,417 (11 studies), 3-36 mo	Moderate[c] due to risk of bias	OR 0.88 (0.74-1.06)	77 per 1,000	9 fewer per 1,000 (from 20 fewer to 4 more)
Mortality all-cause mortality	6,417 (11 studies), 3-36 mo	Moderate[c] due to risk of bias	OR 0.82 (0.62-1.09)	87 per 1,000	15 fewer per 1,000 (from 32 fewer to 7 more)

See Table 1-3 legends for expansion of abbreviations.
[a]Time frame in months.
[b]Defined by individual studies.
[c]Flaws in study design, most commonly lack of blinding.
[d]Significant heterogeneity in pooled analysis ($I^2 = 52.6\%$).

monitoring (Table 6, Table S6). These benefits are seen most prominently in PSM rather than PST groups and possibly in patients with mechanical heart valves rather than other indications.[72] The largest RCT of PST (n = 2,915), the Home INR Study (THINRS), demonstrated no advantage in clinical outcomes vs laboratory-based monitoring but did show modest, significant improvements in patient satisfaction with anticoagulant therapy and quality of life.[73] Data from a pooled analysis also show better patient satisfaction, quality of life, or both with PST/PSM, but these results are difficult to interpret because of the wide range and variable quality of the outcome measures used.[71]

Pooled results from RCTs show only modest (weighted mean difference, 1.50%; 95% CI, −0.63%-3.63%), nonsignificant improvement in TTR with ST/PSM compared with usual laboratory-based monitoring.[71] The frequency of INR testing was considerably higher with PST/PSM compared with usual laboratory-based monitoring, with a mean of 22 to 24 more INR tests annually compared with control groups.[72]

Resource utilization is relevant when considering whether to recommend widespread use of PST/PSM. Some analyses have deemed PST/PSM to be cost-effective,[74-76] whereas others have not.[68,69,77] Higher costs with PST/PSM are driven largely by the cost of test strips and increased testing frequency.[77] However, the increased convenience that PST/PSM offers, particularly to those who travel frequently or who live remotely from testing facilities, can result in lower personal costs for individual patients.[77]

Successful PST/PSM requires well-trained, highly motivated patients. In most RCTs, more than one-half of patients were excluded because of physical limitations, inability to demonstrate competence with POC devices, apprehension about self-care, or patient refusal.[71] Furthermore, up to 25% of patients randomized to PST/PSM withdrew prior to study completion.[67] THINRS was more promising in that ~80% were able to pass a PST competency assessment, but 16% switched from PST to the clinic testing group during the study.[73]

Recommendation

3.6. For patients treated with VKAs who are motivated and can demonstrate competency in self-management strategies, including the self-testing equipment, we suggest PSM rather than usual outpatient INR monitoring (Grade 2B)**.**

For all other patients, we suggest monitoring that includes the safeguards in our best practice statement 3.5.

3.7 Dosing Decision Support

There have been many reports of experience with paper nomograms and computer programs used to assist with VKA dosing.[46,78-97] These dosing adjuncts have been studied at the initiation of therapy (no prior VKA doses) and during the maintenance phase of therapy and were compared with dose decisions made without the use of decision support (manual dosing). Both nomogram/computer-assisted and manual dosing were performed by experienced anticoagulation providers in some studies[78,86,87,90,91] and by providers without specialized training (eg, trainee physicians, house staff, regular physician, nurses) in others.[46,79-85,88,89,92-95]

Decision support-guided dosing (paper nomograms or computer programs) performed no better than manual dosing during initiation of VKA therapy in pooled analyses of available RCTs (Table 7, Table S7). Pooled analyses of RCTs evaluating decision support-guided dosing during maintenance therapy (all were computer-assisted dosing programs) revealed a mean TTR improvement of 4.5% (95% CI, 2.4%-6.7%) compared with no decision support. Although statistically

Table 7—*[Section 3.7] Dosing Decision Support Compared With Manual Dosing for VKA Therapy*[78-80,82,86-88,90-92,94]

Outcomes	No. of Participants (studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]	
				Risk With Manual Dosing	Risk Difference With Dosing Decision Support (95% CI)
Thromboembolism, initiation variously defined	503 (4 studies), 3 mo	Low[b,c] due to risk of bias, imprecision	RR 0.61 (0.27-1.37)	63 per 1,000	63 fewer per 1,000 (from 46 fewer to 23 more)
Major bleeding, initiation variously defined	926 (7 studies[d]), 1-3 mo	Low[b,c] due to risk of bias, imprecision	RR 0.43 (0.17-1.09)	30 per 1,000	17 fewer per 1,000 (from 25 fewer to 3 more)
Mortality, initiation all-cause mortality	748 (5 studies[e]), 1-3 mo	Low[b,c] due to risk of bias, imprecision	RR 0.73 (0.36-1.46)	44 per 1,000	12 fewer per 1,000 (from 28 fewer to 20 more)
Thromboembolism, maintenance variously defined	14,213 (7 studies[f]), 1-12 mo	Moderate[b] due to risk of bias	RR 0.9 (0.7-1.17)	17 per 1,000	2 fewer per 1,000 (from 5 fewer to 3 more)
Major bleeding, maintenance variously defined	14,035 (5 studies[g]), 4.8-12 mo	Moderate[b] due to risk of bias	RR 0.92 (0.71-1.21)	15 per 1,000	1 fewer per 1,000 (from 4 fewer to 3 more)
Mortality, maintenance all cause mortality	14,044 (5 studies[h]), 4.8-12 mo	Moderate[b] due to risk of bias	RR 1.07 (0.78-1.48)	10 per 1,000	1 more per 1,000 (from 2 fewer to 5 more)

See Table 1-3 legends for expansion of abbreviations.
[a]Time frame in days to months.
[b]Most studies were unblinded, including patients, health-care providers, and outcome adjudicators.
[c]CI of relative effect encompasses wide range of benefit and harm.
[d]Asnis et al,[79] Doecke et al,[82] Kovacs et al,[85] Landefeld and Anderson,[46] Vadher et al,[92] van den Bemt et al,[94] and White et al.[95]
[e]Asnis et al,[79] Doecke et al,[82] Kovacs et al,[85] Landefeld and Anderson,[46] and Vadher et al.[92]
[f]Claes et al,[81] Fitzmaurice et al,[83] Fitzmaurice et al,[84] Mitra et al,[88] Poller et al,[91] Vadher et al,[92] and Vadher et al.[93]
[g]Claes et al,[81] Fitzmaurice et al,[83] Fitzmaurice et al,[84] Poller et al,[91] and Vadher et al.[93]
[h]Claes et al,[81] Fitzmaurice et al,[83] Fitzmaurice et al,[84] Poller et al,[89] and Poller et al.[91]

significant, this did not result in improvements in thromboembolism, major bleeding, or mortality outcomes (Table 7). The magnitude of TTR improvement with decision support-guided dosing was smaller when manual dosing in control groups was performed by experienced anticoagulation providers vs providers without specialized training (2.04% vs 8.22%, respectively; no *P* value provided). Higher TTR also has been associated with a paper nomogram in an observational study.[96]

The use of computerized VKA dosing decision support reduces the time taken to dose each patient (mean time for computer-assisted dosing, 94 s; [95% CI, 66-123 s]; manual dosing, 149 s [95% CI, 102-196 s]).[97] This difference is unlikely to be clinically meaningful except in high-volume AMS locations.[84,92,93] Inexperienced anticoagulation providers have safely used decision support-guided dosing.[84,92,93] Although the computer-assisted dosing software is expensive, an economic analysis of the largest computer-assisted dosing RCT concluded that investment in computer-assisted dosing could represent good value if per-patient costs of dosing were reduced.[97]

Recommendation

3.7. For dosing decisions during maintenance VKA therapy, we suggest using validated decision support tools (paper nomograms or computerized dosing programs) rather than no decision support (Grade 2C)**.**

Remarks: Inexperienced prescribers may be more likely to improve prescribing with use of decision support tools than experienced prescribers.

3.8 VKA Drug Interactions to Avoid

Previous systematic reviews addressing drug interactions with VKAs have examined INR results as outcomes and included case reports as evidence.[98] Through a literature review, we sought evidence generated from 1996 to early 2011, looking for randomized trials with >50 patients per group or for large observational studies reporting on clinical outcomes (hemorrhage or VTE) related to drug interactions with VKAs. Our research identified 21 relevant studies. One meta-analysis of RCTs, one prospective cohort study, and many large health database studies were included. A meta-analysis of 10 RCTs (n = 4,180) compared VKA plus aspirin vs VKA alone and showed a reduced rate of arterial thromboembolism (OR, 0.66; 95% CI, 0.52-0.84). However, these benefits were limited to patients with a mechanical heart valve (OR, 0.27; 95% CI, 0.15-0.49), whereas the five studies that dealt with atrial fibrillation and cardiac disease showed no benefit with the combination.[99] Major bleeding was increased in the meta-analysis regardless of the indication for the combination of VKA plus aspirin vs VKA alone (OR, 1.43; 95% CI, 1.00-2.02).

The remaining nonexperimental studies, which varied in size from 53 bleeding events to >13,000 events,

measured hemorrhage as the clinical outcome. In general, the quality of evidence from these studies was low. The VKA studied in ~70% of the reports was warfarin. There was sufficient consistency in statistically significant increased rates of bleeding to be concerned about three main therapeutic drug categories. As noted in Table 8, nonsteroidal antiinflammatory drugs (NSAIDs), both nonselective and cyclooxygenase (COX)-2 selective; antiplatelet agents; and some antibiotics are associated with an increased risk of bleeding in patients taking VKAs.

For nonselective NSAIDs, studies reported ORs or risk ratios (RRs) from 1.9 (95% CI, 1.4-3.7) to 4.6 (95% CI, 3.3-6.5).[100-103,105,118] In addition, two studies reported a higher risk of bleeding with nonselective NSAIDs compared with COX-2-selective NSAIDs.[101,104] There was less consistency in the relationship between COX-2-selective NSAIDs plus VKAs vs VKA alone and bleeding outcomes, varying from a nonsignificant RR of 1.4 (95% CI, 0.44-4.30) to a significant OR of 3.1 (95% CI, 1.4-6.7).[100-103] Antiplatelet agents, either undifferentiated, aspirin alone, or clopidogrel alone, were associated with increased rates of bleeding, with estimates of risk from an OR of 1.5 (95% CI, 1.05-2.22) to a hazard ratio (HR) of 3.1 (95% CI, 2.3-3.9).[102,105,105-111] Aspirin plus clopidogrel plus VKA compared with VKA alone was associated with an HR of 3.70 (95% CI, 2.89-4.76).[108]

Data addressing interactions of antibiotics from multiple large database studies present a somewhat confusing picture. However, there are sufficient studies to suggest a risk of increased bleeding with cotrimoxazole (OR, 2.54 [95% CI, 2.08-3.10]; RR, 5.1 [95% CI, 2.1-12.3])[112,113,115] and quinolones (OR, 1.55 [95% CI, 1.30-1.86]; RR, 5.9 [95% CI, 1.9-18.6]).[105,112,113,115] There is a suggestion that cephalosporins (ignoring the anomalously high RR provided for cefradine), metronidazole, amoxicillin, amoxicillin/clavulanic acid, doxycycline, and fluconazole may have some impact on bleeding risk, but these drugs in general are insufficiently studied.[112-114] Similarly, some studies suggest that selective serotonin reuptake inhibitors, tramadol, acetaminophen, coenzyme Q, and ginger may increase the risk of bleeding, but these also require confirmation.[103,105,106,116,117]

Recommendations

3.8. For patients taking VKAs, we suggest avoiding concomitant treatment with NSAIDs, including COX-2-selective NSAIDs, and certain antibiotics (Grade 2C)**.**

For patients taking VKAs, we suggest avoiding concomitant treatment with antiplatelet agents except in situations where benefit is known or is highly likely to be greater than harm from bleeding, such as patients with mechanical valves, patients with acute coronary syndrome, or patients with recent coronary stents or bypass surgery (Grade 2C)**.**

4.0 VKA—Monitoring

4.1 Optimal Therapeutic INR Range

The desired effect of VKA on the prothrombin time, expressed as INR, can be provided as a therapeutic range (eg, INR 2.0-3.0) or a therapeutic target (eg, INR 2.5). The former provides information on INR values considered acceptable for the patient, whereas the latter is intended to induce those managing anticoagulant therapy to strive for an ideal level.

In a systematic review of 19 studies (one RCT, five with analysis of INR-specific outcomes from RCTs, and 13 observational studies) reporting clinical outcomes in at least three discrete INR ranges and including > 80,000 patients, the lowest rate of a composite outcome of major hemorrhage and symptomatic thromboembolism was seen with INR 2.0 to 3.0.[119] Compared with INR 2.0 to 3.0, the RR for the composite outcome was 2.4 (95% CI, 1.9-3.1) for INR < 2 and 1.8 (95% CI, 1.2-2.6) for INR 3.0 to 5.0. For INR > 5, the RR was 11.9 (95% CI, 6.0-23.4) based on 13 studies for bleeding and only one study for thromboembolism. The evidence profiles are shown separately for comparisons of INR 2.0 to 3.0 vs INR 3.0 to 5.0 (Table 9, Table S8) vs INR < 2.0 (Table 10, Table S9). The definition of major bleeding differed among studies, and the type of thromboembolic events varied according to the studied indication for VKA. However, the pattern of relative risks was consistent among atrial fibrillation, valvular heart disease, and other indications taken together.

Patients with an increased risk of thromboembolic complications are those with (1) a mechanical mitral valve; (2) a mechanical aortic valve in combination with atrial fibrillation, anterior-apical ST-segment elevation myocardial infarction, left atrial enlargement, low ejection fraction, or hypercoagulable state; and (3) caged-ball or caged-disk valve or thromboembolic complications while in INR 2.0 to 3.0. These subsets of patients are traditionally, although with lack of evidence, treated at a higher-intensity INR 2.5 to 3.5 (see Whitlock et al[120] in this supplement).

4.1.1 Low-Intensity VKA for Patients With VTE: Low-intensity treatment with VKA corresponds to INR 1.5 to 1.9/2.0 and is of interest because of the possibility that it might cause less bleeding than conventional intensity (INR 2.0-3.0). In addition, given a wider margin of safety from excessive anticoagulation, laboratory

Table 8—*[Section 3.8] Drug Interactions With VKAs[a]: Drug Families Associated With Increased Risk of Bleeding*

Interacting Drug	Summary Effect on Bleeding (95% CI)[b]	Study
NSAIDS		
NSNSAIDs	OR 1.9 (1.4-3.7)	Battistella et al[100]
	HR 3.6 (2.3-5.6)	Cheetham et al[101]
	RR 1.33 (0.78-2.25)	Delaney et al[102]
	OR 2.6 (1.6-4.2)	Hauta-Ato et al[103]
	OR 3.01 (1.42-6.37)	Knijff-Dutmer et al[104,a]
	RR 2.6-6.5[c]	Penning-van Beest et al[105,a]
	OR 4.6 (3.3-6.5)[d]	Schalekamp et al[106]
	NSNSAID vs COX-2 OR 3.07 (1.18-8.03)	Knijff-Dutmer et al[104,a]
	NSNSAIDs vs COX-2 HR 3.7 (1.4-9.6)	Cheetham et al[101]
COX-2-selective NSAIDs	OR 1.7-2.4[e]	Battistella et al[100]
	HR 1.7 (0.6-4.8)	Cheetham et al[101]
	RR 1.37 (0.44-4.30)	Delaney et al[102]
	OR 3.1 (1.4-6.7)	Hauta-Aho et al[103]
Antiplatelet agents		
Aspirin	OR 1.43 (1.00-2.02)[f]	Dentali et al[99]
	RR 2.23 (1.46-3.41)	Delaney et al[102]
	IR 0.08/patient-y vs 0.06 for warfarin alone	Buresly et al[107]
	HR 1.83 (1.72-1.96)	Hansen et al[108]
	RR 3.0 (1.0-9.4)	Penning-van Beest et al[105,a]
Clopidogrel	HR 3.08 (2.3-3.9)	Hansen et al[108]
Aspirin plus clopidogrel	HR 3.70 (2.89-4.76)	Hansen et al[108]
Antiplatelet agents (any antiplatelet)	OR 2.06 (1.01-4.36)	Johnson et al[109]
	OR 1.53 (1.05-2.22)	Shireman et al[110]
	RR 1.76 (1.05-2.95)	Toyoda et al[111]
Antibiotics		
Cephalexin	OR 1.38 (1.10-1.73)	Schelleman et al[112]
Cefradine	RR 43.0 (10.7-172.4)	Penning-van Beest et al[113,a]
Cephalosporins	OR 1.16 (1.04-1.29)	Zhang et al[114]
Metronidazole	OR 1.58 (1.32-1.89)	Zhang et al[114]
Cotrimoxazole	OR 3.84 (2.33-6.33)	Fischer et al[115]
	OR 2.54 (2.08-3.10)	Schelleman et al[112]
	RR 5.1 (2.1-12.3)	Penning-van Beest et al[113,a,g]
	Cotrimox vs cephalexin OR 1.68 (1.21-2.33)	Schelleman et al[112]
Ciprofloxacin	OR 1.94 (1.28-2.95)	Fischer et al[115]
	OR 1.62 (1.31-1.99)	Schelleman et al[112]
	RR 3.2 (1.3-7.7)	Penning-van Beest et al[113,a]
Levofloxacin	OR 1.55 (1.30-1.86)	Schelleman et al[112]
Norfloxacin	RR 5.9 (1.9-18.6)	Penning-van Beest et al[105,a]
Amoxycillin	OR 1.28 (1.03-1.58)	Schelleman et al[112]
	RR 3.1 (1.6-6.3)	Penning-van Beest et al[113,a]
Amoxycillin/clavulanic acid	RR 4.4 (2.5-7.8)	Penning-van Beest et al[113,a,g]
Doxycycline	RR 2.6 (1.2-4.8)	Penning-van Beest et al[113,a]
Fluconazole	OR 1.89 (1.35-2.64)	Schelleman et al[112]
	Fluconazole vs cephalexin OR 2.09 (1.34-3.26)	Schelleman et al[112]
Other		
SSRIs	OR 2.6 (1.5-4.3)	Hauta-Aho et al[103]
	OR 1.7 (1.1-2.5)[h]	Schalekamp et al[106,a]
	OR 1.1 (0.9-1.4) to 1.2 (0.8-1.7); NS	Kurdyak et al[116]
Tramadol	RR 3.3 (1.1-10.4)	Penning-van Beest et al[105,a]
Complementary medicines	Coenzyme Q10 (OR 3.69, 95% CI 1.88-7.24) and ginger (OR 3.20, 95% CI 2.42-4.24).	Shalansky et al[117]

COX = cyclooxygenase; IR = incidence rate; NSNSAID = nonselective nonsteroidal antiinflammatory drug; SSRI = selective serotonin reuptake inhibitor. See Table 1 and 3 legends for expansion of other abbreviations.
[a]Study VKAs were warfarin, phenprocoumon, and acenocoumarol.
[b]Unless stated, refers to drug plus VKA vs VKA alone.
[c]Diclofenac (RR, 2.6) and naproxen (RR, 6.5) studied separately.
[d]OR is for GI bleeding, whereas OR for non-GI bleeding is 1.7 (95% CI, 1.3-2.2).
[e]Separate OR given for celecoxib (1.7) and rofecoxib (2.4); both statistically significant.
[f]Dentali et al[99] meta-analysis of randomized clinical trials.
[g]Data duplication between two study publications; therefore, more conservative estimate used.
[h]Only statistically significant for non-GI bleeding; not significant for GI bleeding or intracranial bleeding.

Table 9—*[Section 4.1.1] Optimal Therapeutic INR Range: Higher Target vs 2 to 3*[119]

Outcomes	No. of Participants, (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]	
				Risk With INR 2-3	Risk Difference With INR 3-5 (95% CI)
Major hemorrhage per 100 patient-y, various definitions	76,646 (17 studies[b]), 1.8 y	Low[c,d] due to risk of bias, dose-response gradient	RR 2.7 (1.8-3.9)	6 per 1,000	10 more per 1,000 (from 5 more to 17 more)
Thromboembolism per 100 patient-y, various definitions	835 (10 studies[e])	Very low[f,g] due to risk of bias, inconsistency	RR 0.9 (0.6-1.3)	Study population	
				46 per 1,000	5 fewer per 1,000 (from 18 fewer to 14 more)
				Moderate	
				50 per 1,000	5 fewer per 1,000 (from 20 fewer to 15 more)

See Table 1-3 legends for expansion of abbreviations.
[a]Time frame in days to months.
[b]Six studies had a randomized controlled trial design.
[c]The majority of studies (eight) were retrospective cohorts.
[d]It is biologically plausible that with increased intensity there will be more bleeding.
[e]One study had a randomized control design.
[f]Three of four studies had a retrospective cohort design.
[g]Thromboembolic events were more frequent with an INR of 2 to 3 in two studies, less frequent in one study, and similar in one study.

monitoring intervals could perhaps be increased to decrease the burden of therapy on the patient. Two RCTs, both blinded, investigated the efficacy and safety of low-intensity VKA in patients with unprovoked VTE.[121,122] Patients were recruited after having received initial conventional-intensity anticoagulation for months to years. Kearon et al[121] compared low intensity with conventional intensity in 738 patients and found a higher risk of recurrent VTE without any reduction of bleeding events in patients treated with low-intensity VKA. Ridker et al[122] compared low-intensity warfarin with placebo in 508 patients and observed a reduction of recurrent VTE with active treatment without any significant increase in bleeding.

In conclusion, the benefit of low-intensity VKA in terms of reduced risk of bleeding is uncertain because of these inconsistent results. The second benefit of reduced frequency of monitoring is attainable also with conventional-intensity VKA for patients with a stable INR, as reviewed in section 2.1. Thus, the proposed advantage of lower-intensity VKA therapy in the extended-treatment phase is questionable.

4.1.2 Low-Intensity VKA for Patients With Atrial Fibrillation: For stroke prophylaxis in atrial fibrillation, two less-intensive alternatives to conventional-intensity VKA have been studied. Minidose or low-intensity fixed-dose VKA, usually corresponding to 1.25 mg (0.5-3 mg) warfarin daily, was given with the intention to minimize the need for laboratory monitoring. A meta-analysis of four randomized trials with 2,753 patients showed that minidose warfarin was inferior to conventional-intensity VKA with regard to thrombotic events (RR, 0.50; 95% CI, 0.25-0.97). Results were uncertain for major hemorrhage (RR, 1.23; 95% CI, 0.67-2.27) or fatal bleeding (RR, 0.97; 95% CI, 0.27-3.54).[123]

Low-intensity VKA with a therapeutic range of INR 1.5 to 2.0 (or 2.1 in one study) has been compared head to head with conventional intensity, without the addition of aspirin, in two randomized trials.[124,125] One study from Japan was stopped prematurely after an excess of major hemorrhages in the conventional-intensity group.[124] A similar trend was seen in a separate study from Italy.[123] Neither study showed a difference in stroke or deaths. The mean age of the patients differed; 65 years in the Japanese study[124] and 80 years in the Italian trial.[125] The pooled results show that there is a significant reduction of nonfatal extracranial hemorrhages with low-intensity VKA (OR, 0.21; 95% CI, 0.06-0.6) without any appreciable increase in the rate of stroke or mortality.

A case-control study in patients with atrial fibrillation suggested that the risk of stroke increases at INR $<$ 2.0.[126] Compared with an INR of 2.0, the OR for stroke was 2.0 (95% CI, 1.6-2.4) at an INR of 1.7 and 3.3 (95% CI, 2.4-4.6) at an INR of 1.5. There is a trade-off that pits a substantial relative risk reduction of stroke ($\sim$80%) with INR 1.5 to 2.0 compared with INR $<$ 1.2,[127,128] with a greater risk of thromboembolic events with INR 1.4 to 1.7 compared with INR 2.0 to 2.5 (OR, 3.72; 95% CI, 2.67-5.19) (Anticoagulation and Risk Factors in Atrial Fibrillation [ATRIA] cohort).[129] In this study, there was no evidence for a reduced risk for intracranial hemorrhage at INR $<$ 2.0 compared with 2.0 to 3.5. The event

Table 10—*[Section 4.1.2] Optimal Therapeutic INR Range: Lower Target vs 2 to 3*[119]

Outcomes	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With INR 2-3	Anticipated Absolute Effects: Risk Difference With INR < 2 (95% CI)
Major hemorrhage per 100 patient-y, various definitions	78,493 (17 studies[a])	Very low[a,b] due to risk of bias, inconsistency	RR 1.1 (0.7-1.7)	Study population	
				6 per 1,000	1 more per 1,000 (from 2 fewer to 4 more)
				Moderate	
				23 per 1,000	2 more per 1,000 (from 7 fewer to 16 more)
Thromboembolism per 100 patient-y	827 (4 studies[c])	Moderate[d-f] due to risk of bias, large effect, dose-response gradient	RR 3.5 (2.8-4.4)	Study population	
				46 per 1,000	115 more per 1,000 (from 83 more to 157 more)
				Moderate	
				40 per 1,000	100 more per 1,000 (from 72 more to 136 more)

See Table 1-3 legends for expansion of abbreviations.
[a]Eight of the studies were retrospective cohorts.
[b]Four studies showed higher risk of bleeding, with INR < 2.
[c]Only one study had a randomized control design.
[d]No explanation was provided.
[e]At least 2.8 times more frequent thromboembolism.
[f]It is biologically plausible with more thromboembolism at a lower INR.

rate of intracranial hemorrhage is low with long-term VKA therapy (0.3% per year),[130] thus very large numbers are required to detect a difference. There was a reduction of major, nonfatal extracranial hemorrhage with low- vs standard-intensity VKA in the two RCTs (OR, 0.21; 95% CI, 0.06-0.6), and this could be important for patients with a documented bleeding diathesis.

Recommendation

4.1. For patients treated with VKAs, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) rather than a lower (INR < 2) or higher (INR 3.0-5.0) range (Grade 1B)**.**

4.2 Therapeutic Range for High-Risk Groups

The most common therapeutic range for treatment with VKAs is INR 2.0 to 3.0, as discussed previously. Higher intensity for patients with a mechanical mitral valve or with a mechanical aortic valve in combination with other risk factors is discussed in Whitlock et al[120] in this supplement.

Patients with severe thrombophilia (antiphospholipid syndrome, deficiency of protein C, protein S, or antithrombin homozygous factor V Leiden) who have thromboembolic events have an increased risk of recurrent VTE compared with those without thrombophilia or with mild defects (eg, heterozygous factor V Leiden) in the absence of anticoagulant treatment. It is not clear to what extent this is true while taking VKAs. Case series of patients with deficiency of any of the natural inhibitors (protein C, protein S, antithrombin) or with the common factor V Leiden or prothrombin gene polymorphisms have not provided any indication that moderate intensity (INR 2.0-3.0) is inadequate for these conditions.

In retrospective studies, moderate-intensity anticoagulation often was insufficient to prevent arterial or venous thrombosis in patients with antiphospholipid antibodies. Many of the patients in these studies were recruited from specialized centers for patients with rheumatic disease,[131-133] which may be a different population than those with primary antiphospholipid syndrome (ie, thromboembolism without identified underlying disease).

A systematic review compared the efficacy and safety of different approaches of secondary prophylaxis against thromboembolism in patients with antiphospholipid antibodies based on 16 studies (two RCTs, two subgroup analyses from RCTs, three prospective cohorts or subgroup analysis, and nine retrospective cohorts or subgroup analyses).[134] There were more fatal thromboembolic events than fatal hemorrhages (18 vs one), and the risk of thrombotic events was inversely related to the INR value in the observational studies but not in the RCTs. In many of the studies, only a single laboratory test had been used to confirm the syndrome, whereas according to current criteria (revised Sapporo criteria), at least two positive tests should be recorded with an interval of at least 12 weeks.[135]

The results of the two RCTs[136,137] are shown in Table 10 (Table S10). Both studies were small, with 110 patients randomized to higher-intensity (INR 3.0-4.0 or INR 3.0-4.5) and 110 randomized to moderate-intensity (INR 2.0-3.0) warfarin therapy. Three patients with nonembolic arterial disease were assigned to aspirin alone (not included in Table 11[138]). Because the CIs for the relative risk are wide and risk of bias is substantial, the quality of evidence is low.

Patients with cancer and VTE have a higher risk of recurrent events during anticoagulant therapy than patients without cancer.[139,140] When such a breakthrough event occurs, an intensification of treatment sometimes is suggested.[141] There are no published aggregate data on the effectiveness and safety of intensified treatment with VKA, only single-patient case reports. Dose escalation of LMWH appeared effective to prevent further recurrence in a retrospective review of 70 patients.[142]

Recommendation

4.2. For patients with antiphospholipid syndrome with previous arterial or venous thromboembolism, we suggest VKA therapy titrated to a moderate-intensity INR range (INR 2.0-3.0) rather than higher intensity (INR 3.0-4.5) (Grade 2B)**.**

5.0 VKA—Discontinuation of Therapy

There is a theoretical concern that abrupt VKA discontinuation may result in a temporary hypercoagulable state due to an imbalance in the rates of normalization of activity of the coagulation factors II, VII, IX, and X on the one hand and the natural inhibitors protein C and protein S on the other.[143] Five small controlled trials (total n = 217) have addressed this issue.[144-147] The primary outcomes of four of the studies were laboratory results suggestive of a hypercoagulable state[144,145,147,148] and produced inconsistent results. Elevations tended to persist for 8 to 9 weeks, regardless of discontinuation strategy, suggesting an unmasked prothrombotic state in the absence of anticoagulant protection rather than a rebound phenomenon associated with abrupt discontinuation.

The thromboembolism event rate appeared similar between groups across the five studies (Table 12, Table S11).[144-148] The only major hemorrhage occurred

Table 11—*[Section 4.2] High-Intensity VKA Compared With Moderate-Intensity VKA for Patients With Antiphospholipid Syndrome*[136,137]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Moderate-Intensity VKA	Anticipated Absolute Effects: Risk Difference With High-Intensity VKA (95% CI)
Thromboembolism objective confirmation	220 (2 studies[a]), 3 y	Very low[b,c] due to risk of bias, indirectness, and imprecision	OR 2.33 (0.82-6.66)	Study population[d]	
				45 per 1,000[2]	54 more per 1,000 (from 8 fewer to 195 more)
				Low[d]	
				50 per 1,000[a]	59 more per 1,000 (from 9 fewer to 210 more)
				High[d]	
				700 per 1,000[a]	145 more per 1,000 (from 43 fewer to 240 more)
Major bleeding	220 (2 studies[e]), 3 y	Moderate[f] due to imprecision	OR 0.70 (0.23-2.16)	Study population	
				64 per 1,000[a]	18 fewer per 1,000 (from 48 fewer to 64 more)
				Low	
				25 per 1,000[a]	7 fewer per 1,000 (from 19 fewer to 27 more)
				High	
				100 per 1,000[a]	28 fewer per 1,000 (from 75 fewer to 94 more)
Mortality all-cause mortality	220 (2 studies), 3 y	Moderate[f] due to imprecision	OR 1.51 (0.3-7.72)	18 per 1,000	9 more per 1,000 (from 13 fewer to 107 more)

See Table 1 and 2 legends for expansion of abbreviations.
[a]In the study by Finazzi et al,[137] three patients with nonembolic arterial thrombosis received, as planned, only aspirin. They had no events and have not been included here.
[b]The study by Finazzi et al[137] was open label.
[c]Both studies were designed to show superiority of the more intensive regimen, not equivalence. The 95% CI includes both benefit and significant harm.
[d]Low of 5% from Schulman et al[138]; high of 70% from Khamashta et al.[131]
[e]The types of major hemorrhage were not disclosed.
[f]The 95% CI includes both benefit and significant harm.

Table 12—*[Section 5.0] Gradual Withdrawal Compared With Abrupt Withdrawal for Patients Taking VKAs for at Least One Month*[144-148]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]: Risk With Abrupt Withdrawal	Anticipated Absolute Effects[a]: Risk Difference With Gradual Withdrawal (95% CI)
Thromboembolism imaging diagnostics	217 (5 studies), 3 mo	Low[b,c] due to risk of bias, imprecision	OR 0.96 (0.42-2.18)	126 per 1,000[d]	4 fewer per 1,000 (from 69 fewer to 113 more)
Mortality all-cause mortality	217 (5 studies), 1 mo	Very low[b,c] due to risk of bias, imprecision	OR 0 (0.01-5.6)	9 per 1,000	9 fewer per 1,000 (from 9 fewer to 39 more)[d]
Major hemorrhage	217 (5 studies), 1 mo	Very low[b,c] due to risk of bias, imprecision	OR 1 (0.1-5.6)	9 per 1,000	0 fewer per 1,000 (from 8 fewer to 39 more)[d]

See Table 1 and 2 legends for expansion of abbreviations.

[a]Time frame is weeks.

[b]Unclear whether allocation was adequate in Tardy et al,[148] de Groot et al,[145] and Ascani et al.[144] In Michaels and Beamish,[146] it was according to year of birth. Unclear whether allocation was concealed in Tardy, de Groot, and Ascani; it was not concealed in Michaels. Clinicians and patients were not blinded in de Groot, Michaels, Palareti et al,[147] or Ascani.

[c]Very small patient groups and few events.

[d]There is no better source than these trials, so low or high estimates are not provided.

in the gradual withdrawal group. Gradual discontinuation of VKA is likely to be more confusing and inconvenient for the patient.

Recommendation

5.0. For patients eligible to discontinue treatment with VKA, we suggest abrupt discontinuation rather than gradual tapering of the dose to discontinuation (Grade 2C)**.**

6.0 Parenteral Anticoagulants

6.1 UFH—Dose Adjustment by Weight

Five RCTs compared initial IV UFH dosing according to a weight-based nomogram with a fixed-dose approach.[149-153] The study by Jaff et al[151] was excluded because no weight-adjusted group for the initial bolus was included. The study by Toth and Voll[153] was excluded because the fixed dose varied by treating physician, and thromboembolic or bleeding complications were not specified. In the remaining three RCTs a total of 292 patients were randomized to either weight based or fixed dose initially. The fixed dose was a bolus of 70 to 80 units/kg followed by an infusion rate of 15 to 18 units/kg per h. Activated partial thromboplastin time (aPTT) values were monitored, and UFH dose titrated to the therapeutic range.[149,150,152] In one of the studies, a POC device for measuring aPTT was used.[149] Patients with acute coronary syndromes[150] or mixed diagnosed conditions, including VTE,[149,152] were recruited. Study follow-up periods ranged from 48 h[149,150] to 3 months.[152] The weight-based and fixed-dose approaches achieved similar therapeutic aPTTs during the first 24 to 48 h. Patient-important adverse events, which were not well defined, were few; thromboembolism in eight vs two (OR, 0.22; 95% CI, 0.02-1.13) in the fixed-dose vs weight-adjusted group and only one major bleed (fixed-dose group) (Table 13, Table S12). These results suggest that weight-adjusted dosing and fixed dosing of IV UFH are similar in outcomes. Small numbers of clinical events and failure to specify the timing of thromboembolic complications are major limitations of available studies.

Either regimen can be monitored with plasma heparin levels, but there is no evidence to suggest that monitoring improves clinical outcomes. The evidence linking plasma heparin levels of 0.3 to 0.7 International Units/mL anti-Xa activity by the amidolytic assay to the occurrence of either bleeding or thrombosis is also of low quality.[152]

Recommendation

6.1. For patients starting IV UFH, we suggest that the initial bolus and the initial rate of the continuous infusion be weight adjusted (bolus 80 units/kg followed by 18 units/kg per h for VTE; bolus 70 units/kg followed by 15 units/kg per h for cardiac or stroke patients) or a fixed-dose (bolus 5,000 units followed by 1,000 units/h) rather than alternative regimens (Grade 2C)**.**

6.2 UFH—Dose Management of SC UFH

Treatment with UFH has traditionally been monitored with aPTT plasma tests, whether administered by IV or SC. The SC treatment regimens for UFH generally were based on a fixed initial dose.[154] In contrast, short-term treatment with LMWH is given without any laboratory monitoring because the pharmacokinetic characteristics are believed to be more predictable than for UFH. Studies of SC UFH have not compared weight-based dosing

Table 13—*[Section 6.1] UFH: Weight-Based Nomogram Compared With Fixed Initial Dose for Patients With Thromboembolic Disease*[149,150,152]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]	
				Risk With Fixed Initial Dose	Risk Difference With UFH-Weight-Based Nomogram (95% CI)
Thromboembolism	292 (3 studies), 2-90 d[b]	Low[c,d] due to risk of bias and imprecision	OR 0.22 (0.02-1.13)[e]	57 per 1,000[f]	44 fewer per 1,000 (from 56 fewer to 7 more)
Major hemorrhage	179 (2 studies[g]), 1 wk	Very low[c,d] due to risk of bias and imprecision	Not estimable[h]	11 per 1,000	10 fewer per 1,000 (from 30 fewer to 10 more)

See Table 1 and 2 legends for expansion of abbreviations.
[a]Time frame is days to weeks.
[b]Only Raschke et al[152] collected data over a 3-mo period.
[c]The studies did not use blinding.
[d]None of the studies was powered for clinical outcomes, which were few and poorly reported with regard to type and timing.
[e]Fisher exact test.
[f]Two of the eight events occurred after discontinuation of warfarin.
[g]Becker et al[149] reported 2% bleeding without specifying allocation group or type of bleeding.
[h]Zero events in control group; 95% CI on OR not estimable.

vs fixed dosing with or without the use of aPTT monitoring. Weight-adjusted SC UFH monitored with aPTT has been compared with SC LMWH in three RCTs (n = 937) with similar clinical outcome results as follows: recurrent VTE (OR, 1.13; 95% CI, 0.52-2.46), major bleeding (OR, 1.28; 95% CI, 0.42-4.09), and death (OR, 1.34; (95% CI, 0.62-2.93).[155]

One RCT in patients with VTE has compared the use of weight-adjusted dosing of SC UFH to weight-based dosing of LMWH without monitoring.[156] The SC UFH was administered at an initial dose of 333 units/kg followed by a dose of 250 units/kg bid; subsequent UFH dosing was kept constant. Clinical outcomes were similar between the SC UFH and LMWH groups (Table 14, Table S13).

Because all of the evidence for initial dosing and monitoring of SC UFH is indirect, the quality of evidence for any recommendation is very low. Outpatient use of SC UFH while transitioning to VKA treatment derives some benefit from the elimination of daily blood work. Treatment with UFH often is preferred for patients with severe renal insufficiency, where there is a risk for accumulation of LMWH or fondaparinux.

Recommendation

6.2. For outpatients with VTE treated with SC UFH, we suggest weight-adjusted dosing (first dose 333 units/kg, then 250 units/kg) without monitoring rather than fixed or weight-adjusted dosing with monitoring (Grade 2C)**.**

Table 14—*[Section 6.2] UFH: Weight-Adjusted Nonmonitored UFH SC Compared With Weight-Adjusted Nonmonitored LMWH SC for Outpatients With Acute VTE*[156]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]	
				Risk With Weight-Adjusted Nonmonitored LMWH SC	Risk Difference With Weight-Adjusted Nonmonitored UFH SC (95% CI)
Recurrent VTE objectively measured with same method as for index event	697 (1 study), 3 mo	Low[b,c] due to indirectness and imprecision	OR 1.11 (0.49-2.52)	34 per 1,000	4 more per 1,000 (from 17 fewer to 48 more)
Major bleeding by ISTH criteria	697 (1 study), 3 mo	Low[b,c] due to indirectness and imprecision	OR 0.5 (0.17-1.34)	34 per 1,000	17 fewer per 1,000 (from 28 fewer to 11 more)
Mortality	697 (1 study), 3 mo	Low[b,c] due to indirectness and imprecision	OR 0.83 (0.43-1.57)	62 per 1,000	10 fewer per 1,000 (from 35 fewer to 32 more)

ISTH = International Society on Thrombosis and Haemostasis; SC = subcutaneous. See Table 1 and 2 legends for expansion of other abbreviations.
[a]Time frame is days to weeks.
[b]The comparison should actually be vs fixed-dose UFH SC with monitoring, but weight-adjusted UFH SC has only been compared directly with weight-adjusted LMWH. Thus, the comparison is indirect.
[c]Because of premature discontinuation, the study was not powered to demonstrate equivalence.

7.0 LMWH—Dosing

7.1 Should the Therapeutic Dose of LMWH Be Modified for Decreased Renal Function?

LMWH, as opposed to UFH, is primarily eliminated through renal excretion. We found no RCTs comparing a standard, body-weight-adjusted dose to a reduced dose of LMWH in severe renal insufficiency, defined as creatinine clearance < 30 mL/min.

A meta-analysis of 18 observational studies or subgroup analyses of studies using therapeutic doses of LMWH provides some indirect evidence on this patient population.[157] On the basis of four of the studies, this review suggested that standard doses of LMWH led to higher peak levels of anti-factor Xa in patients with a creatinine clearance < 30 mL/min compared with those with a creatinine clearance > 30 mL/min. On the basis of three studies, when the dose of LMWH was reduced for severe renal failure, no such difference in peak level was observed. All of these seven studies used enoxaparin, so there are insufficient data to comment on other LMWHs. In addition, the relevance of anti-factor Xa levels is unclear; several studies have failed to show a relationship between the anti-Xa levels and bleeding.[158-160]

For patients treated with LMWH, the risk of bleeding was generally higher in patients with a creatinine clearance < 30 mL/min compared with patients with a creatinine clearance > 30 mL/min (5.0% vs 2.4%; OR, 2.25; 95% CI, 1.19-4.27; $P = .013$).[157] However, because the risk of bleeding is also increased when patients with severe renal failure are treated with UFH,[161] the problem may be the renal function rather than the dosing regimen. Four observational studies in the review using enoxaparin suggested that lowering doses for severe renal impairment may reduce the incidence of bleeding (Table 15).[157] The dose adjustment was either empirical or to 0.5 vs the standard 1 mg/kg bid of enoxaparin. There are insufficient data on VTE outcomes. Overall, the evidence is indirect and from studies of low quality and provides no advice on how LMWH should be reduced if the decision is to reduce.

Recommendation

7.1. For patients receiving therapeutic LMWH who have severe renal insufficiency (calculated creatinine clearance < 30 mL/min), we suggest a reduction of the dose rather than using standard doses (Grade 2C)**.**

8.0 Fondaparinux—Dosing

8.1 Fondaparinux Dose Management by Weight

Doses of heparins for the treatment of thrombosis often are administered according to patient body weight for both LMWH and UFH. Both total body weight and lean body weight have been used. In clinical trials, patients with morbid obesity (> 120-130 kg) often have been excluded. We did not identify any studies comparing weight-adjusted dosing of fondaparinux to standard doses not adjusted for weight. Two randomized trials for symptomatic venous thrombosis[162,163] used doses adjusted for the total body weight of the patient (5.0, 7.5, or 10 mg in patients weighing < 50, 50-100, or > 100 kg, respectively). These trials—one in DVT,[162] one in PE[163]—compared fondaparinux to enoxaparin and UFH, respectively. A separate study was a subgroup analysis comparing the 3-month incidence of recurrent VTE or major bleeding events in a subset of patients weighing < 100 kg and > 100 kg.[164] The incidences of recurrence and major bleeds appeared to be similar for each patient subset of weight and BMI for patients treated with fondaparinux; VTE occurred in 75 of 1,946 (3.9%) nonobese patients vs 10 of 251 (4%) obese patients, and major bleeds occurred in 25 of 1,993 (1.3%) nonobese patients vs in one of 248 (0.4%) in obese patients. This subgroup analysis has several limitations (no tests for interaction, small number of obese patients, unclear definitions of major bleeds) and provides only low-quality evidence. There are insufficient data on patient s with low body weight to make any recommendation or suggestion regarding dose adjustment for these patients.

Recommendation

8.1. For patients with VTE and body weight over 100 kg, we suggest that the treatment dose of fondaparinux be increased from the usual 7.5 mg to 10 mg daily subcutaneously (Grade 2C)**.**

Table 15—*[Section 7.1] Risk of Bleeding With Enoxaparin According to the Calculated Creatinine Clearance*

	Bleeding Rate CalCrCl ≤ 30, n/N (%)	Bleeding Rate CalCrCl > 30, n/N (%)	OR (95% CI)
Studies where dose was unadjusted for CalCrCl	17/206 (8.3)	96/4,081 (2.4)	3.88 (1.78-8.45)
Studies where dose was adjusted for CalCrCl	1/106 (0.9)	5/265 (1.9)	0.58 (0.09-3.78)

CalCrCl = calculated creatinine clearance.

9.0 Prevention and Management of Anticoagulant Complications

9.1 Vitamin K for Patients Taking VKAs With High INRs Without Bleeding

The risk of bleeding increases significantly when the INR exceeds 4.5.[165] In a retrospective review, patients with mechanical heart valves had a risk of adverse events that increased logarithmically from two per 100 patient-years at INR 2.5 to 4.9, to 4.8 per 100 patient-years for INR 5 to 5.5, then to 75 per 100 patient-years for INR ≥ 6.5.[166] Similarly, a case-control analysis of adults sustaining intracerebral bleeding while on warfarin noted a doubling of intracerebral bleeding for every 0.5-s increment in prothrombin time (approximately every 1-point increase in INR).[167]

When the INR is supratherapeutic without evidence of bleeding, strategies used to lower the INR have included withholding VKA, adjusting the dose of VKA, and providing some dose of vitamin K. Vitamin K shortens the time to return to normal INR.[168-170] A 2006 meta-analysis found that administration of vitamin K orally or by IV was more likely to reverse overanticoagulation (INR > 4) at 24 h compared with simply withholding VKA.[171]

INR 4.5 to 10 Without Bleeding: Four RCTs compared vitamin K with placebo for patients with INR 4.5 to 10, and all reported on major bleeding as an outcome (Table 16, Table S14).[168,169,172,173] Pooled analysis suggests that rates of major bleeding were similar over 1 to 3 months of follow-up (2% [10 of 452] of patients receiving vitamin K vs 0.8% [four of 4/471] in the placebo group). Thromboembolism as reported in three of the studies[168,169,172] and occurred in five of 423 patients in the vitamin K group vs four of 441 patients in the placebo group. In summary, although vitamin K use may reverse supratherapeutic INRs more rapidly, there is no evidence of benefit for patient-important outcomes.

INR > 10 Without Bleeding: We found no randomized trials that tested treatment strategies in this patient group. A prospective case series of 107 patients with INR > 10 and without evidence of bleeding showed that 2.5 mg of oral vitamin K resulted in a low rate of observed major bleeding by 90 days (3.9%; 95% CI, 1.1-9.7).[174] Another retrospective study of 89 patients found that such patients given oral vitamin K 2 mg were less likely to still have an INR > 5 by day 3 compared with those who only had warfarin withheld (11.1% vs 46.7%).[175] Patient preferences and clinical assessment of risks of thrombosis and bleeding are likely important factors in determining whether to give vitamin K. In summary, the benefit and harm of vitamin K administration for patients with an INR > 10 and no bleeding are unclear, although the risk of bleeding may be substantial.

Recommendations

9.1.

(a) For patients taking VKAs with INRs between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B**).**

Table 16—*[Section 9.1] Vitamin K vs Only Withholding VKA for Patients Taking Warfarin With an Elevated INR (4.5-10) Without Evidence of Bleeding*[a,168,169,172,173]

Outcomes	No. of Participants (studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]: Risk With Only Holding VKA	Anticipated Absolute Effects[a]: Risk Difference With Vitamin K (95% CI)
Major bleeding	923 (4 studies[b]), 1-3 mo[c]	Moderate[d,e] due to imprecision	OR 2.6 (0.8-9.8)	8 per 1,000	13 more per 1,000 (from 2 fewer to 69 more)
Thromboembolism	864 (3 studies[f]), 1-3 mo[c]	Moderate[d,e] due to imprecision	OR 1.3 (0.3-6.6)	9 per 1,000	3 more per 1,000 (from 6 fewer to 48 more)
Mortality all-cause mortality	863 (3 studies[f]), 1-3 mo[c]	Moderate[d,e] due to imprecision	OR 1.3 (0.6-2.9)	29 per 1,000	9 more per 1,000 (from 12 fewer to 51 more)

See Table 1 and 2 legends for expansion of other abbreviations. See Table 1 through 3 legends for expansion of other abbreviations.
[a]Time frame is days.
INR 6.0-12.0 in Ageno et al.[173]
[b]None of the studies specified whether any bleeding events were fatal or intracranial.
[c]Follow-up was 3 mo in both studies by Crowther et al.[168,169]
[d]Two small studies, Ageno et al[172] and Ageno et al,[173] were open label.
[e]Wide CIs encompass both benefit and significant harm.
[f]Ageno et al[173] did not report thromboembolism, and Ageno et al[172] did not report deaths.

(b) For patients taking VKAs with INRs > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered (Grade 2C)**.**

9.2 Clinical Prediction Rules for Bleeding While Taking VKA

The annual incidence of warfarin-associated major bleeding is estimated at 1% to 3%.[176] Clinicians continually struggle with estimating and weighing patient risk of thromboembolic events with risk of major bleeding. A clinical prediction rule for an individual's risk of bleeding while taking warfarin or other VKAs would be very useful if prediction of low risk reassured patients sufficiently to start VKA therapy or, more importantly, if prediction of high risk of bleeding was sufficiently accurate to withhold VKA therapy.

A 2007 systematic review by Dahri and Loewen[177] examined studies developing clinical prediction rules for bleeding while taking warfarin for any indication. Seven studies were included, with the primary outcome being the ability of the clinical prediction rule to distinguish between patients at high vs low risk of experiencing major bleeding.[6,178-183] The performance of a rule was considered moderate if the likelihood ratio for a high score to predict major bleeding was > 5.0 and strong if it was > 10.0.[184,185] Two variants of the same clinical prediction rule had a likelihood ratio of ∼9.[178,179] The independently validated mOBRI (modified Outpatient Bleeding Risk Index)[179] includes the following predictors: age ≥ 65 years, history of stroke, GI bleed in the past 2 weeks, and at least one of the following comorbidities: recent myocardial infarction, hematocrit level < 30%, creatinine level > 1.5 mg/dL, or diabetes mellitus. One point is given for each of the four risk factor categories, with high risk defined as ≥ 3 points.

Since the 2007 systematic review, two additional clinical prediction rules have been published.[186-188] Table 17[179-183,186-190] summarizes the clinical prediction rules according to (1) the proportion of patients classified as high risk, (2) the risk of major bleeding measured in that subset, and (3) the annual risk of stroke required to prefer an alternative therapy with a lower risk of bleeding for patients with atrial fibrillation. The column on stroke risk required is based on the assumption of a stronger preference for avoiding stroke compared with avoiding a major bleeding event by a factor of 3:1.[2] Using this metric, most of the rules would suggest a prohibitively high risk of major bleeding only for patients with a $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack) score of 0, a group for whom VKA therapy might not be preferred anyway. However, for patients with a greater preference of avoiding bleeding events compared with stroke, use of $CHADS_2$ score along with a clinical prediction rule, such as mOBRI, may provide some prognostic guidance. Similarly, the studies involving a population treated for VTE do not identify a group with a risk of bleeding sufficiently high to preclude secondary prophylaxis with VKA. A clinical prediction rule that could predict an individual's risk of both benefit and harm at the time of initiation of VKA therapy would be desirable, but none has been validated.[191]

Recommendation

9.2. For patients initiating VKA therapy, we suggest against the routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy (Grade 2C)**.**

9.3 Treatment of Anticoagulant-Related Bleeding

When patients present with major bleeding due to VKA use, rapid reversal of anticoagulation is desirable, particularly if the bleeding is life threatening. Several products are available to assist, with treatment, often combining vitamin K with one of prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), or recombinant factor VIIa. FFP has the disadvantage of potential allergic reaction or transmission of infection, preparation time, and higher volume. PCC and recombinant factor VIIa are more rapidly concentrated with less infection transmission risk but have not been compared with FFP in adequately powered RCTs.

Vitamin K is given to sustain the effects of the other products because of the relatively short half-lives of the latter. In emergency situations, vitamin K 10 mg IV instead of given orally is recommended because of its more rapid onset.[24,171,192] IV injection of vitamin K is reported to cause anaphylaxis in three of 100,000 patients, resulting in advice to infuse slowly.[193] In one RCT of patients with INR 6 to 10 without bleeding, IV injection (0.5 mg) compared with po (2.5 mg) phytonadione more rapidly brought the INR back to therapeutic range (11 of 24 patients vs 0 of 23 patients at 6 h).[192] However, by 24 h, the mean INR in both groups was similar. In a second RCT of patients with INR 6 to 10, vitamin K 0.5 mg IV led to faster resolution than vitamin K 3 mg SC, with an INR < 5 in 95% vs 45% of patients and a mean INR of 3.7 vs 5.4 at 24 h.[194] Accordingly, SC injection is not recommended.

Several studies have compared products in addition to vitamin K, three of which reported rates of intracranial hemorrhage. A small case series of 17 patients compared the use of FFP and three-factor PCC; all patients received vitamin K.[195] The mean INR decreased from 2.83 to 1.22 within 4.8 h in patients receiving PCC vs from 2.97 to 1.74 within 7.3 h for those receiving FFP ($P < .001$). The reaction level

Table 17—*[Section 9.2] Clinical Prediction Rules for VKA-Associated Major Bleeding*

Study Acronym or Authors	Sample, No.	Population	Follow-up Duration, Mean	Proportion With High Risk	Major Bleeding Events in High-Risk Group	Stroke Risk Required to Avoid VKA[a]
mOBRI[179]	Derivation: 565 Validation: 264	VTE, valves, other	Derivation: 2 y Validation: 6-7 y	Derivation: 6.1% Validation: 6.9% ($\geq$3 p)	Derivation: 3 m: 23% 12 m: 48% Validation: 3 m: 6% 12 m: 30%	N/A[b]
mOBRI—validation[180]	Validation 1,269	50% AF, 50% other diagnoses	1 y	15.4%	Patients with AF: 12.3%/y	$<$4%/y
mOBRI—validation[6]	Validation: 222	VTE	1.5 y	1%	0%	N/A[b]
Kuijer et al[182]	Derivation: 241 Validation: 780	VTE	3 mo	21% 19% ($>$3 p)	Derivation: 14%/3 mo Validation: 7%/3 mo	N/A[b]
$HEMORR_2HAGES$[181]	1,604 discharged on warfarin	AF	0.83 y	16.3% (3-4 p)	8.8%/y	$<$3%/y
Shireman et al[183]	Derivation: 19,875 Validation: 6,470	AF, warfarin naïve	3 mo	Validation: 3.4% (score $\geq$ 2.19)	Validation: 5.4%/3 mo[c]	$<$1.8% first 3 mo
RIETE registry[187]	Derivation: 13,057 Validation: 6,572	VTE	3 mo	Derivation: 5.8% Validation: 5.2%	Derivation: 7.3%/3 mo Validation: 6.2%/3 mo	N/A[b]
HAS-BLED[186]	Derivation: 3,381 Validation: 3,071	AF	1 y	Derivation: 1.7% Validation: 7.9% ($\geq$3 p)	Derivation: 20%/y Validation: 4.9%/y	Validation: $<$1.7%/y
HAS-BLED—separate validation[188]	Validation: 3,665	AF	499 d?	18.7%	6.7%/y	$<$2%/y

AF = atrial fibrillation; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly ($>$65), drugs/alcohol concomitantly; $HEMORR_2HAGES$ = hepatic or renal disease, ethanol use, malignancy, reduced platelet count, re-bleeding, hypertension, anemia, genetic factors, elevated risk of fall including neuropsychiatric disease, stroke; mOBRI = modified Outpatient Bleeding Risk Index; p = total points within the CPR; RIETE = Computerized Registry of Patients with Venous Thromboembolism. See Table 1 legend for expansion of abbreviation.

[a]Based on assumption that the dysutility of a stroke is three times that of a major bleeding event, where most major bleeding is GI.

[b]For patients with VTE, the alternative would be no therapy, which can be estimated to result in a risk of recurrence of 22% to 29%[189,190] during the first 3 mo. With the assumption that the dysutility of a recurrence corresponds to the dysutility of a major bleeding event, where the majority consists of GI bleeding, the risk of major bleeding would have to be at least the same during the first 3 mo to avoid VKA.

[c]This risk normally will decrease after the first 3 mo of treatment.

grade, used to assess symptoms and signs of intracerebral hemorrhage, suggested less progression in those receiving PCC (0.2 vs 1.9 grades on a scale of 1-8) ($P < .05$). Another small before-after study of 12 patients reported that the six patients receiving three-factor PCC compared with six age- and sex-matched historical controls given FFP had a mean INR correction time of 41 min for PCC vs 115 min for FFP.[196]

Finally, a small RCT compared factor IX complex concentrate (four-factor PCC) plus FFP vs FFP alone in 13 patients (five in factor IX concentrate and eight in FFP).[197] Factor IX concentrate plus FFP corrected the INR more quickly than FFP alone (2.95 vs 8.9 h, $P < .01$). In addition, five of eight patients in the FFP-alone group experienced significant fluid overload complications, despite monitoring of central venous pressure and the use of furosemide, compared with no reported complications in the combination group.

FFP has also been compared with four-factor PCC in patients undergoing cardiopulmonary bypass surgery.[198] Forty patients admitted to the hospital for urgent or semiurgent cardiac surgery who were taking oral anticoagulants (INR 2.1-7.8) were randomized, 20 to each treatment. Seven PCC patients vs no FFP patients had an INR < 1.5 by 15 min ($P = .007$); an additional six PCC vs four FFP patients had this level an hour later ($P = .70$).

Three very small case series addressed the use of recombinant factor VIIa. In a series of 13 patients presenting with bleeding (four patients), requiring rapid reversal for interventions (five patients), or with an INR > 10 and not good candidates for FFP (four patients), all had a reduction in INR after administration but to variable degrees.[199] Use in four patients presenting with major bleeding (two with spinal cord hemorrhages and two with intracerebral hemorrhages) resulted in a normal INR within 2 h, with no complications reported.[200] Finally, in a series of seven patients with acute intracranial hemorrhage while taking warfarin, the mean INR was reduced from 2.7 pre-recombinant factor VIIa to 1.1 afterward. Several of the patients also received vitamin K and FFP. Five of the patients survived with severe disability, and two died.[201] Factor concentrates including PCC are expensive and, therefore, not available in some jurisdictions.

Recommendations

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor PCC rather than with plasma (Grade 2C)**.**

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C)**.**

9.4 Investigating Anticoagulant-Associated Bleeding

No randomized trials have addressed different strategies of investigating bleeding in patients taking anticoagulants. The topic is of great practical importance in patient management, but the evidence found was not of sufficient quality to make a recommendation. One small case-control study found the monthly incidence and prevalence of hematuria to be 0.05% and 3.2% in those taking anticoagulants vs 0.08% and 4.8% for those in the control group.[202] Subsequent diagnosis of cancer was also similar at two of 32 patients in the anticoagulation group compared with one of 11 patients in the control group. Two small case series of patients investigated for anticoagulant-associated hematuria found two of 30 and four of 24, respectively, had neoplastic disease.[203,204] A retrospective analysis of all patients presenting with gross hematuria over a 9-year period while taking anticoagulant or aspirin therapy found that 25% (six of 25) of those patients presenting with hematuria were found to have a tumor.[205]

Several studies addressed the question of GI bleeding. A retrospective series of 166 patients presenting with lower GI bleeding, with 100 of the patients taking an antiplatelet or anticoagulant and 66 not, found that nine of 88 (10.2%) patients taking anticoagulants had colon cancer compared with two of 62 (3.2%) not taking anticoagulants.[206] Another analysis of 98 patients taking warfarin who presented to a Veterans Affairs hospital with acute GI bleeding found on endoscopy that 52 of the 71 had upper-GI lesions, whereas on colonoscopy, 26 of 41 had lesions, including five cancers.[207] In summary, although the data are of low quality, they suggest that there might be sufficient incidence of pathologic causes for VKA-associated hematuria or GI bleeding to warrant investigation.

10.0 Other

10.1 Intensive Patient Education and Anticoagulation Outcomes

Intensive patient education (defined as dedicated patient education sessions beyond the usual VKA information distributed by pamphlet or the patient's usual provider) has been proposed to reduce adverse events related to anticoagulation and to improve TTR. Although better patient knowledge of anticoagulation has been associated with improved INR control, these were no randomized trials, and INRs were surrogate outcomes.[208,209]

Seven RCTs (n = 1,195) compared supplemental patient education with usual care and provided some data on clinical outcomes.[210-216] Patient age varied widely (18-91 years), and the indications for VKA therapy included atrial fibrillation and VTE. Six of

the studies were based in anticoagulation clinics. Educational interventions varied among studies. Several allowed for only one teaching session delivered in person by a health-care professional, by means of a video presentation of a physician-patient interaction, or by a patient-administered self-guided instruction booklet.[215,216] Others had repeated interaction with patients at daily intervals on a ward until discharge or at weekly or bimonthly intervals in outpatient clinics.[210,212,213] The curricula covered similar content, including indications for VKAs, benefits and risks, the importance of INR surveillance, drug interactions, the effect of diet, and information on dose management. The amount and type of education in the control arms were unclear. The length of follow-up ranged from 3 to 6 months.

The quality of evidence based on these studies is low primarily because of limitations in design and imprecision for the clinical outcomes. In pooling data from three of the studies that reported clinical outcomes in a similar manner, there was no significant difference between supplemental patient education and usual care (VTE RR, 0.61 [95% CI, 0.06-6.56]; hemorrhage RR, 0.92 [95% CI, 0.04-20.56]).[210,212,213] TTR was reported in four trials and was similar between groups (mean difference, 2.03%; 95% CI, −2.79-6.86).[210-212,214] In the single study where the difference in intensity of education was marked (described as minimal vs daily intensive education for mean of 8 days), there was no difference in outcomes, including TTR.[212] Although we found no compelling evidence favoring intensive patient education over standard patient education practices, the panel believed that a specific recommendation could not be made at this time.

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Dr Holbrook: served as Topic Editor.
Dr Schulman: served as Deputy Editor.
Dr Witt: served as a panelist.
Dr Vandvik: served as a panelist.
Dr Fish: served as a frontline clinician.
Dr Kovacs: served as a panelist.
Dr Svensson: served as a panelist.
Dr Veenstra: served as a resource consultant.
Dr Crowther: served as a panelist.
Dr Guyatt: served as guideline editor and contributed to the editing of this manuscript.

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References

1. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e44S-e88S.
2. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):53S-70S.
3. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e419S-e494S.
4. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e227S-e277S.
5. Monkman K, Lazo-Langner A, Kovacs MJ. A 10 mg warfarin initiation nomogram is safe and effective in outpatients starting oral anticoagulant therapy for venous thromboembolism. *Thromb Res*. 2009;124(3):275-280.
6. Wells PS, Le Gala G, Tierney S, Carrier M. Practical application of the 10-mg warfarin initiation nomogram. *Blood Coagul Fibrinolysis*. 2009;20:403-408.
7. Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med*. 1999;159(1):46-48.
8. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med*. 1997;126(2):133-136.
9. Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. A randomized, double-blind, controlled trial. *Ann Intern Med*. 2003;138(9):714-719.

10. Quiroz R, Gerhard-Herman M, Kosowsky JM, et al. Comparison of a single end point to determine optimal initial warfarin dosing (5 mg versus 10 mg) for venous thromboembolism. *Am J Cardiol*. 2006;98(4):535-537.
11. Schulman S, Lockner D, Bergström K, Blombäck M. Intensive initial oral anticoagulation and shorter heparin treatment in deep vein thrombosis. *Thromb Haemost*. 1984;52(3):276-280.
12. Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. *Clin Med Res*. 2005;3(3):137-145.
13. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. *Clin Pharmacol Ther*. 2008;83(3):460-470.
14. Anderson JL, Horne BD, Stevens SM, et al; Couma-Gen Investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation*. 2007;116(22):2563-2570.
15. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. *Pharmacogenet Genomics*. 2009;19(3):226-234.
16. Heneghan C, Tyndel S, Bankhead C, et al. Optimal loading dose for the initiation of warfarin: a systematic review. *BMC Cardiovasc Disord*. 2010;10(1):18.
17. Meckley LM, Gudgeon JM, Anderson JL, Williams MS, Veenstra DL. A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing. *Pharmacoeconomics*. 2010;28(1):61-74.
18. Patrick AR, Avorn J, Choudhry NK. Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2009;2(5):429-436.
19. Eckman MH, Rosand J, Greenberg SM, Gage BF. Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation. *Ann Intern Med*. 2009;150(2):73-83.
20. Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med*. 1990;322(18):1260-1264.
21. Leroyer C, Bressollette L, Oger E, et al; The ANTENOX Study Group. Early versus delayed introduction of oral vitamin K antagonists in combination with low-molecular-weight heparin in the treatment of deep vein thrombosis. a randomized clinical trial. *Haemostasis*. 1998;28(2):70-77.
22. Mohiuddin SM, Hilleman DE, Destache CJ, Stoysich AM, Gannon JM, Sketch MH Sr. Efficacy and safety of early versus late initiation of warfarin during heparin therapy in acute thromboembolism. *Am Heart J*. 1992;123(3):729-732.
23. Fihn SD, McDonell MB, Vermes D, et al; National Consortium of Anticoagulation Clinics. A computerized intervention to improve timing of outpatient follow-up: a multicenter randomized trial in patients treated with warfarin. *J Gen Intern Med*. 1994;9(3):131-139.
24. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133(suppl 6):160S-198S.
25. Rose AJ, Ozonoff A, Berlowitz DR, Henault LE, Hylek EM. Warfarin dose management affects INR control. *J Thromb Haemost*. 2009;7(1):94-101.
26. Rose AJ, Ozonoff A, Berlowitz DR, Ash AS, Reisman JI, Hylek EM. Reexamining the recommended follow-up interval after obtaining an in-range international normalized ratio value: results from the Veterans Affairs study to improve anticoagulation. *Chest*. 2011;140(2):359-365.
27. Fitzmaurice DA. Oral anticoagulation should be managed in the community with treatment aimed at standard therapeutic targets and increased recall intervals. *J Thromb Haemost*. 2008;6(10):1645-1646.
28. Guidelines on oral anticoagulation: third edition. *Br J Haematol*. 1998;101(2):374-387.
29. Lidstone V, Janes S, Stross P. INR: Intervals of measurement can safely extend to 14 weeks. *Clin Lab Haematol*. 2000;22(5):291-293.
30. Shalev V, Rogowski O, Shimron O, et al. The interval between prothrombin time tests and the quality of oral anticoagulants treatment in patients with chronic atrial fibrillation. *Thromb Res*. 2007;120(2):201-206.
31. Witt DM, Delate T, Clark NP, et al; Warped Consortium. Twelve-month outcomes and predictors of very stable INR control in prevalent warfarin users. *J Thromb Haemost*. 2010;8(4):744-749.
32. Witt DM, Delate T, Clark NP, et al; Warfarin Associated Research Projects and other EnDeavors (WARPED) Consortium. Outcomes and predictors of very stable INR control during chronic anticoagulation therapy. *Blood*. 2009;114(5):952-956.
33. Rose AJ, Ozonoff A, Henault LE, Hylek EM. Warfarin for atrial fibrillation in community-based practise. *J Thromb Haemost*. 2008;6(10):1647-1654.
34. Pengo V, Barbero F, Biasiolo A, Pegoraro C, Cucchini U, Iliceto S. A comparison between six- and four-week intervals in surveillance of oral anticoagulant treatment. *Am J Clin Pathol*. 2003;120(6):944-947.
35. Schulman S, Parpia S, Stewart C, Rudd-Scott L, Julian J, Levine M. Warfarin dose assessment every 4 weeks versus every 12 weeks in patients with stable international normalized ratios: a randomized trial. *Ann Intern Med*. 2011;155(10):653-659.
36. Rose AJ, Hylek EM, Berlowitz DR, Ash AS, Reisman JI, Ozonoff A. Prompt repeat testing after out-of-range INR values: a quality indicator for anticoagulation care. *Circ Cardiovasc Qual Outcomes*. 2011;4(3):276-282.
37. Schulman S, Melinyshyn A, Ennis D, Rudd-Scott L. Single-dose adjustment versus no adjustment of warfarin in stably anticoagulated patients with an occasional international normalized ratio (INR) out of range. *Thromb Res*. 2010;125(5):393-397.
38. Banet GA, Waterman AD, Milligan PE, Gatchel SK, Gage BF. Warfarin dose reduction vs watchful waiting for mild elevations in the international normalized ratio. *Chest*. 2003;123(2):499-503.
39. Clark NP, Witt DM, Delate T, et al; Warfarin-Associated Research Projects and Other Endeavors Consortium. Thromboembolic consequences of subtherapeutic anticoagulation in patients stabilized on warfarin therapy: the low INR study. *Pharmacotherapy*. 2008;28(8):960-967.
40. Dentali F, Riva N, Malato A, Saccullo G, Siragusa S, Ageno W. Incidence of thromboembolic complications in patients with mechanical heart valves with a subtherapeutic international normalized ratio. *J Thorac Cardiovasc Surg*. 2009;137(1):91-93.
41. Kim KH, Choi WS, Lee JH, Lee H, Yang DH, Chae SC. Relationship between dietary vitamin K intake and the stability of anticoagulation effect in patients taking long-term warfarin. *Thromb Haemost*. 2010;104(4):755-759.
42. Rombouts EK, Rosendaal FR, Van Der Meer FJM. Daily vitamin K supplementation improves anticoagulant stability. *J Thromb Haemost*. 2007;5(10):2043-2048.

43. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. *Blood*. 2007;109(6):2419-2423.
44. Gebuis EPA, Rosendaal FR, van Meegen E, van der Meer FJM. Vitamin K1 supplementation to improve the stability of anticoagulation therapy with vitamin K antagonists: a dose-finding study. *Haematologica*. 2011;96(4):583-589.
45. Lalonde L, Martineau J, Blais N, et al. Is long-term pharmacist-managed anticoagulation service efficient? A pragmatic randomized controlled trial. *Am Heart J*. 2008; 156(1):148-154.
46. Landefeld CS, Anderson PA. Guideline-based consultation to prevent anticoagulant-related bleeding. A randomized, controlled trial in a teaching hospital. *Ann Intern Med*. 1992;116(10):829-837.
47. Matchar DB, Samsa GP, Cohen SJ, Oddone EZ, Jurgelski AE. Improving the quality of anticoagulation of patients with atrial fibrillation in managed care organizations: results of the managing anticoagulation services trial. *Am J Med*. 2002; 113(1):42-51.
48. Wilson SJ-A, Wells PS, Kovacs MJ, et al. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. *CMAJ*. 2003;169(4):293-298.
49. Airee A, Guirguis AB, Mohammad RA. Clinical outcomes and pharmacists' acceptance of a community hospital's anticoagulation management service utilizing decentralized clinical staff pharmacists. *Ann Pharmacother*. 2009;43(4):621-628.
50. Biscup-Horn PJ, Streiff MB, Ulbrich TR, Nesbit TW, Shermock KM. Impact of an inpatient anticoagulation management service on clinical outcomes. *Ann Pharmacother*. 2008;42(6):777-782.
51. Bond CA, Raehl CL. Pharmacist-provided anticoagulation management in United States hospitals: death rates, length of stay, Medicare charges, bleeding complications, and transfusions. *Pharmacotherapy*. 2004;24(8):953-963.
52. Bungard TJ, Gardner L, Archer SL, et al. Evaluation of a pharmacist-managed anticoagulation clinic: Improving patient care. *Open Med*. 2009;3(1):e16-e21.
53. Burns N. Evaluation of warfarin dosing by pharmacists for elderly medical in-patients. *Pharm World Sci*. 2004;26(4): 232-237.
54. Chau T, Rotbard M, King S, Li MM, Leong WA. Implementation and evaluation of a warfarin dosing service for rehabilitation medicine: report from a pilot project. *Can J Hosp Pharm*. 2006;59(1):137-147.
55. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med*. 1998;158(15):1641-1647.
56. Cohen IA, Hutchison TA, Kirking DM, Shue ME. Evaluation of a pharmacist-managed anticoagulation clinic. *J Clin Hosp Pharm*. 1985;10(2):167-175.
57. Cortelazzo S, Finazzi G, Viero P, et al. Thrombotic and hemorrhagic complications in patients with mechanical heart valve prosthesis attending an anticoagulation clinic. *Thromb Haemost*. 1993;69(4):316-320.
58. Dager WE, Branch JM, King JH, et al. Optimization of inpatient warfarin therapy: impact of daily consultation by a pharmacist-managed anticoagulation service. *Ann Pharmacother*. 2000; 34(5):567-572.
59. Ellis RF, Stephens MA, Sharp GB. Evaluation of a pharmacy-managed warfarin-monitoring service to coordinate inpatient and outpatient therapy. *Am J Hosp Pharm*. 1992;49(2):387-394.
60. Locke C, Ravnan SL, Patel R, Uchizono JA. Reduction in warfarin adverse events requiring patient hospitalization after implementation of a pharmacist-managed anticoagulation service. *Pharmacotherapy*. 2005;25(5):685-689.
61. Poon IO, Lal L, Brown EN, Braun UK. The impact of pharmacist-managed oral anticoagulation therapy in older veterans. *J Clin Pharm Ther*. 2007;32(1):21-29.
62. Wallvik J, Själander A, Johansson L, Bjuhr Ö, Jansson JH. Bleeding complications during warfarin treatment in primary healthcare centres compared with anticoagulation clinics. *Scand J Prim Health Care*. 2007;25(2):123-128.
63. Tschol N, Lai DK, Tilley JA, Wong H, Brown GR. Comparison of physician- and pharmacist-managed warfarin sodium treatment in open heart surgery patients. *Can J Cardiol*. 2003;19(12):1413-1417.
64. Wilt VM, Gums JG, Ahmed OI, Moore LM. Outcome analysis of a pharmacist-managed anticoagulation service. *Pharmacotherapy*. 1995;15(6):732-739.
65. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest*. 2005;127(5):1515-1522.
66. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systematic review and metaregression. *Chest*. 2006; 129(5):1155-1166.
67. Garcia-Alamino JM, Ward AM, Alonso-Coello P, et al. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev*. 2010; (4):CD003839.
68. Brown A, Wells P, Jaffey J, et al. *Devices for Point-of-Care Monitoring of Long-Term Oral Anticoagulation Therapy: Clinical and Cost Effectiveness*. Technology overview number 24. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2007.
69. Connock M, Stevens C, Fry-Smith A, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technol Assess*. 2007;11(38): 66.
70. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet*. 2006; 367(9508):404-411.
71. Bloomfield HE, Krause A, Greer N, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med*. 2011;154(7):472-482.
72. Heneghan C, Ward A, Perera R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data [published online ahead of print December 1, 2011]. *Lancet*. doi:10.1016/S0140-6736(11)61294-4.
73. Matchar DB, Jacobson A, Dolor R, et al; THINRS Executive Committee and Site Investigators. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med*. 2010;363(17):1608-1620.
74. Lafata JE, Martin SA, Kaatz S, Ward RE. Anticoagulation clinics and patient self-testing for patients on chronic warfarin therapy: a cost-effectiveness analysis. *J Thromb Thrombolysis*. 2000;9(suppl 1):S13-S19.
75. Medical Advisory Secretariat. Point-of-care international normalized ratio (INR) monitoring devices for patients on long-term oral anticoagulation therapy: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2009;9(12).
76. Regier DA, Sunderji R, Lynd LD, Gin K, Marra CA. Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. *CMAJ*. 2006;174(13):1847-1852.
77. Jowett S, Bryan S, Murray E, et al. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. *Br J Haematol*. 2006;134(6):632-639.

78. Ageno W, Turpie AG. A randomized comparison of a computer-based dosing program with a manual system to monitor oral anticoagulant therapy. *Thromb Res*. 1998;91(5):237-240.
79. Asnis PD, Gardner MJ, Ranawat A, Leitzes AH, Peterson MG, Bass AR. The effectiveness of warfarin dosing from a nomogram compared with house staff dosing. *J Arthroplasty*. 2007;22(2):213-218.
80. Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. *Clin Pharm*. 1987;6(1):37-45.
81. Claes N, Buntinx F, Vijgen J, et al. The Belgian improvement study on oral anticoagulation therapy: a randomized clinical trial. *Eur Heart J*. 2005;26(20):2159-2165.
82. Doecke CJ, Cosh DG, Gallus AS. Standardised initial warfarin treatment: evaluation of initial treatment response and maintenance dose prediction by randomised trial, and risk factors for an excessive warfarin response. *Aust N Z J Med*. 1991;21(3):319-324.
83. Fitzmaurice DA, Hobbs FD, Murray ET, Bradley CP, Holder R. Evaluation of computerized decision support for oral anticoagulation management based in primary care. *Br J Gen Pract*. 1996;46(410):533-535.
84. Fitzmaurice DA, Hobbs FDR, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. *Arch Intern Med*. 2000;160(15):2343-2348.
85. Kovacs MJ, Cruickshank M, Wells PS, et al. Randomized assessment of a warfarin nomogram for initial oral anticoagulation after venous thromboembolic disease. *Haemostasis*. 1998;28(2):62-69.
86. Manotti C, Moia M, Palareti G, Pengo V, Ria L, Dettori AG. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). *Haematologica*. 2001;86(10):1060-1070.
87. Marco F, Sedano C, Bermúdez A, López-Duarte M, Fernández-Fontecha E, Zubizarreta A. A prospective controlled study of a computer-assisted acenocoumarol dosage program. *Pathophysiol Haemost Thromb*. 2003;33(2):59-63.
88. Mitra R, Marciello MA, Brain C, Ahangar B, Burke DT. Efficacy of computer-aided dosing of warfarin among patients in a rehabilitation hospital. *Am J Phys Med Rehabil*. 2005;84(6):423-427.
89. Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. *J Clin Pathol*. 1993;46(4):299-303.
90. Poller L, Shiach CR, MacCallum PK, et al. Multicentre randomised study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation. *Lancet*. 1998;352(9139):1505-1509.
91. Poller L, Keown M, Ibrahim S, et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. *J Thromb Haemost*. 2008;6(6):935-943.
92. Vadher B, Patterson DL, Leaning M. Evaluation of a decision support system for initiation and control of oral anticoagulation in a randomised trial. *BMJ*. 1997;314(7089):1252-1256.
93. Vadher BD, Patterson DLH, Leaning M. Comparison of oral anticoagulant control by a nurse-practitioner using a computer decision-support system with that by clinicians. *Clin Lab Haematol*. 1997;19(3):203-207.
94. van den Bemt PM, Beinema M, van Roon EN, et al. Initiation of oral anticoagulant therapy in orthopedic and surgical patients: an algorithm compared with routine dosing. *Eur J Clin Pharmacol*. 2002;58(3):203-208.
95. White RH, Hong R, Venook AP, et al. Initiation of warfarin therapy: comparison of physician dosing with computer-assisted dosing. *J Gen Intern Med*. 1987;2(3):141-148.
96. Kim YK, Nieuwlaat R, Connolly SJ, et al. Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study. *J Thromb Haemost*. 2010;8(1):101-106.
97. Jowett S, Bryan S, Poller L, et al. The cost-effectiveness of computer-assisted anticoagulant dosage: results from the European Action on Anticoagulation (EAA) multicentre study. *J Thromb Haemost*. 2009;7(9):1482-1490.
98. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165(10):1095-1106.
99. Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med*. 2007;167(2):117-124.
100. Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med*. 2005;165(2):189-192.
101. Cheetham TC, Levy G, Niu F, Bixler F. Gastrointestinal safety of nonsteroidal antiinflammatory drugs and selective cyclooxygenase-2 inhibitors in patients on warfarin. *Ann Pharmacother*. 2009;43(11):1765-1773.
102. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug-drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *CMAJ*. 2007;177(4):347-351.
103. Hauta-Aho M, Tirkkonen T, Vahlberg T, Laine K. The effect of drug interactions on bleeding risk associated with warfarin therapy in hospitalized patients. *Ann Med*. 2009;41(8):619-628.
104. Knijff-Dutmer EA, Van der Palen J, Schut G, Van de Laar MA. The influence of cyclo-oxygenase specificity of non-steroidal anti-inflammatory drugs on bleeding complications in concomitant coumarine users. *QJM*. 2003;96(7):513-520.
105. Penning-van Beest F, Erkens J, Petersen K-U, Koelz HR, Herings R. Main comedications associated with major bleeding during anticoagulant therapy with coumarins. *Eur J Clin Pharmacol*. 2005;61(5-6):439-444.
106. Schalekamp T, Klungel OH, Souverein PC, de Boer A. Increased bleeding risk with concurrent use of selective serotonin reuptake inhibitors and coumarins. *Arch Intern Med*. 2008;168(2):180-185.
107. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med*. 2005;165(7):784-789.
108. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med*. 2010;170(16):1433-1441.
109. Johnson SG, Rogers K, Delate T, Witt DM. Outcomes associated with combined antiplatelet and anticoagulant therapy. *Chest*. 2008;133(4):948-954.
110. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke*. 2004;35(10):2362-2367.
111. Toyoda K, Yasaka M, Iwade K, et al; Bleeding with Antithrombotic Therapy (BAT) Study Group. Dual antithrombotic

therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. *Stroke*. 2008;39(6):1740-1745.

112. Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin Pharmacol Ther*. 2008;84(5):581-588.
113. Penning-van Beest FJA, Koerselman J, Herings RMC. Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants. *J Thromb Haemost*. 2008;6(2): 284-290.
114. Zhang K, Young C, Berger J. Administrative claims analysis of the relationship between warfarin use and risk of hemorrhage including drug-drug and drug-disease interactions. *J Manag Care Pharm*. 2006;12(8):640-648.
115. Fischer HD, Juurlink DN, Mamdani MM, Kopp A, Laupacis A. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. *Arch Intern Med*. 2010; 170(7):617-621.
116. Kurdyak PA, Juurlink DN, Kopp A, Herrmann N, Mamdani MM. Antidepressants, warfarin, and the risk of hemorrhage. *J Clin Psychopharmacol*. 2005;25(6):561-564.
117. Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. *Pharmacotherapy*. 2007;27(9):1237-1247.
118. Knijff-Dutmer EA, Schut GA, van de Laar MA. Concomitant coumarin-NSAID therapy and risk for bleeding. *Ann Pharmacother*. 2003;37(1):12-16.
119. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ*. 2008;179(3):235-244.
120. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl): e576S-e600S.
121. Kearon C, Ginsberg JS, Kovacs MJ, et al; Extended Low-Intensity Anticoagulation for Thrombo-Embolism Investigators. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;349(7):631-639.
122. Ridker PM, Goldhaber SZ, Danielson E, et al; PREVENT Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;348(15):1425-1434.
123. Perret-Guillaume C, Wahl DG. Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose—a meta-analysis. *Thromb Haemost*. 2004;91(2):394-402.
124. Yamaguchi T; Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation : a multicenter, prospective, randomized trial. *Stroke*. 2000;31(4):817-821.
125. Pengo V, Cucchini U, Denas G, et al. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. *Thromb Haemost*. 2010;103(2):442-449.
126. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1996;335(8):540-546.
127. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;348(9028):633-638.
128. Hart RG. Intensity of anticoagulation to prevent stroke in patients with atrial fibrillation. *Ann Intern Med*. 1998; 128(5):408.
129. Singer DE, Chang Y, Fang MC, et al. Should patient characteristics influence target anticoagulation intensity for stroke prevention in nonvalvular atrial fibrillation?: the ATRIA study. *Circ Cardiovasc Qual Outcomes*. 2009;2(4): 297-304.
130. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131(7): 492-501.
131. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med*. 1995;332(15):993-997.
132. Rosove MH, Brewer PM. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann Intern Med*. 1992;117(4):303-308.
133. Ruiz-Irastorza G, Khamashta MA, Hunt BJ, Escudero A, Cuadrado MJ, Hughes GR. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. *Arch Intern Med*. 2002;162(10):1164-1169.
134. Ruiz-Irastorza G, Hunt BJ, Khamashta MA. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. *Arthritis Rheum*. 2007;57(8): 1487-1495.
135. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306.
136. Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med*. 2003;349(12):1133-1138.
137. Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005;3(5):848-853.
138. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. *Am J Med*. 1998:10(4):332-338.
139. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol*. 2000;18(17):3078-3083.
140. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100(10):3484-3488.

141. Imberti D, Di Nisio M, Donati MB, et al; Italian Society for Thrombosis and Haemostasis. Treatment of venous thromboembolism in patients with cancer: Guidelines of the Italian Society for Haemostasis and Thrombosis (SISET). *Thromb Res*. 2009;124(5):e32-e40.
142. Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. *J Thromb Haemost*. 2009; 7(5):760-765.
143. Grip L, Blombäck M, Schulman S. Hypercoagulable state and thromboembolism following warfarin withdrawal in post-myocardial-infarction patients. *Eur Heart J*. 1991; 12(11):1225-1233.
144. Ascani A, Iorio A, Agnelli G. Withdrawal of warfarin after deep vein thrombosis: effects of a low fixed dose on rebound thrombin generation. *Blood Coagul Fibrinolysis*. 1999;10(5):291-295.
145. de Groot MR, Njo TL, van Marwijk Kooy M, Büller HR. Abrupt versus gradual withdrawal of vitamin K antagonist treatment in patients with venous thromboembolic disease: assessment of hypercoagulability and clinical outcome. *Clin Lab*. 2000;46(11-12):575-581.
146. Michaels L, Beamish RE. Relapses of thromboembolic disease after discontinued anticoagulant therapy. A comparison of the incidence after abrupt and after gradual termination of treatment. *Am J Cardiol*. 1967;20(5):670-673.
147. Palareti G, Legnani C, Guazzaloca G, et al. Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants—a prospective study. *Thromb Haemost*. 1994;72(2):222-226.
148. Tardy B, Tardy-Poncet B, Laporte-Simitsidis S, et al. Evolution of blood coagulation and fibrinolysis parameters after abrupt versus gradual withdrawal of acenocoumarol in patients with venous thromboembolism: a double-blind randomized study. *Br J Haematol*. 1997;96(1):174-178.
149. Becker RC, Ball SP, Eisenberg P, et al; Antithrombotic Therapy Consortium Investigators. A randomized, multicenter trial of weight-adjusted intravenous heparin dose titration and point-of-care coagulation monitoring in hospitalized patients with active thromboembolic disease. *Am Heart J*. 1999;137(1):59-71.
150. Hassan WM, Flaker GC, Feutz C, Petroski GF, Smith D. Improved anticoagulation with a weight-adjusted heparin nomogram in patients with acute coronary syndromes: a randomized trial. *J Thromb Thrombolysis*. 1995;2(3):245-249.
151. Jaff MR, Olin JW, Piedmonte M, Pirzada C, Young JR. Heparin administration via nomogram versus a standard approach in venous and arterial thromboembolic disease. *Vasc Med*. 1996;1(2):97-101.
152. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med*. 1993;119(9):874-881.
153. Toth C, Voll C. Validation of a weight-based nomogram for the use of intravenous heparin in transient ischemic attack or stroke. *Stroke*. 2002;33(3):670-674.
154. Hommes DW, Bura A, Mazzolai L, Büller HR, ten Cate JW. Subcutaneous heparin compared with continuous intravenous heparin administration in the initial treatment of deep vein thrombosis. A meta-analysis. *Ann Intern Med*. 1992;116(4):279-284.
155. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease. *Chest*. 2008;133(6 suppl):454S-545S.
156. Kearon C, Ginsberg JS, Julian JA, et al; Fixed-Dose Heparin (FIDO) Investigators. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006;296(8):935-942.
157. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*. 2006;144(9):673-684.
158. Bara L, Leizorovicz A, Picolet H, Samama M; Post-surgery Logiparin Study Group. Correlation between anti-Xa and occurrence of thrombosis and haemorrhage in post-surgical patients treated with either Logiparin (LMWH) or unfractionated heparin. *Thromb Res*. 1992;65(4-5):641-650.
159. Walenga JM, Hoppensteadt D, Fareed J. Laboratory monitoring of the clinical effects of low molecular weight heparins. *Thromb Res*. 1991;14(14S):49-62.
160. Prandoni P, Lensing AW, Büller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet*. 1992;339(8791):441-445.
161. Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al. Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin. *Chest*. 2004;125(3):856-863.
162. Büller HR, Davidson BL, Decousus H, et al; Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*. 2004;140(11):867-873.
163. Büller HR, Davidson BL, Decousus H, et al; Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism [published correction appears in *N Engl J Med*. 2004;350(4):423]. *N Engl J Med*. 2003;349(18):1695-1702.
164. Davidson BL, Büller HR, Decousus H, et al; Matisse Investigators. Effect of obesity on outcomes after fondaparinux, enoxaparin, or heparin treatment for acute venous thromboembolism in the Matisse trials. *J Thromb Haemost*. 2007; 5(6):1191-1194.
165. Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE. Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. *Arch Intern Med*. 2000;160(11):1612-1617.
166. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbroucke JP, Briët E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med*. 1995;333(1):11-17.
167. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med*. 1994;120(11):897-902.
168. Crowther MA, Ageno W, Garcia D, et al. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. *Ann Intern Med*. 2009;150(5):293-300.
169. Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. *Lancet*. 2000;356(9241):1551-1553.
170. Patel RJ, Witt DM, Saseen JJ, Tillman DJ, Wilkinson DS. Randomized, placebo-controlled trial of oral phytonadione for excessive anticoagulation. *Pharmacotherapy*. 2000;20(10): 1159-1166.
171. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'malley PG. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med*. 2006;166(4):391-397.
172. Ageno W, Crowther M, Steidl L, et al. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a

randomized controlled trial. *Thromb Haemost*. 2002;88(1): 48-51.
173. Ageno W, Garcia D, Silingardi M, Galli M, Crowther, M. A randomized trial comparing 1 mg of oral vitamin K with no treatment in the management of warfarin-associated coagulopathy in patients with mechanical heart valves. *J Am Coll Cardiol*. 2005;46(4):730-742.
174. Crowther MA, Garcia D, Ageno W, et al. Oral vitamin K effectively treats international normalised ratio (INR) values in excess of 10. Results of a prospective cohort study. *Thromb Haemost*. 2010;104(1):118-121.
175. Gunther KE, Conway G, Leibach L, Crowther MA. Low-dose oral vitamin K is safe and effective for outpatient management of patients with an INR>10. *Thromb Res*. 2004; 113(3-4):205-209.
176. Schulman S, Beyth RJ, Kearon C, Levine MN; American College of Chest Physicians. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133(suppl 6): 257S-298S.
177. Dahri K, Loewen P. The risk of bleeding with warfarin: a systematic review and performance analysis of clinical prediction rules. *Thromb Haemost*. 2007;98(5):980-987.
178. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med*. 1989; 87(2):144-152.
179. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105(2):91-99.
180. Aspinall SL, DeSanzo BE, Trilli LE, Good CB. Bleeding Risk Index in an anticoagulation clinic. Assessment by indication and implications for care. *J Gen Intern Med*. 2005; 20(11):1008-1013.
181. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-2870.
182. Kuijer PM, Hutten BA, Prins MH, Büller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med*. 1999;159(5): 457-460.
183. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest*. 2006;130(5):1390-1396.
184. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA*. 1994;271(9):703-707.
185. Jaeschke R, Guyatt G, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA*. 1994;271(5):389-391.
186. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100.
187. Ruíz-Giménez N, Suárez C, González R, et al; RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost*. 2008;100(1):26-31.
188. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;57(2):173-180.
189. Lagerstedt CI, Olsson CG, Fagher BO, Öqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet*. 1985; 2(8454):515-518.
190. Rosenbeck-Hansen JV, Valdorf-Hansen F, Dige-Petersen H, Hansen W. En kontrolleret undersøgelse af antikoagulationsbehandlingens effekt ved dyb venetrombose og lungeemboli. *Nord Med*. 1968;80:1305-1306.
191. Pereira JA, Holbrook AM, Thabane L, van Walraven C. Methods for individualizing the benefit and harm of warfarin. *Can J Clin Pharmacol*. 2007;14(2):e128.15.
192. Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. *Arch Intern Med*. 2003;163(20):2469-2473.
193. Fiore LD, Scola MA, Cantillon CE, Brophy MT. Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis*. 2001;11(2):175-183.
194. Nee R, Doppenschmidt D, Donovan DJ, Andrews TC. Intravenous versus subcutaneous vitamin K1 in reversing excessive oral anticoagulation. *Am J Cardiol*. 1999;83(2): 286-288.
195. Fredriksson K, Norrving B, Strömblad LG. Emergency reversal of anticoagulation after intracerebral hemorrhage. *Stroke*. 1992;23(7):972-977.
196. Cartmill M, Dolan G, Byrne JL, Byrne PO. Prothrombin complex concentrate for oral anticoagulant reversal in neurosurgical emergencies. *Br J Neurosurg*. 2000;14(5): 458-461.
197. Boulis NM, Bobek MP, Schmaier A, Hoff JT. Use of factor IX complex in warfarin-related intracranial hemorrhage. *Neurosurgery*. 1999;45(5):1113-1119.
198. Demeyere R, Gillardin S, Arnout J, Strengers PFW. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. *Vox Sang*. 2010;99(3):251-260.
199. Deveras RAE, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med*. 2002;137(11):884-888.
200. Lin J, Hanigan WC, Tarantino M, Wang J. The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings. *J Neurosurg*. 2003;98(4):737-740.
201. Freeman WD, Brott TG, Barrett KM, et al. Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. *Mayo Clin Proc*. 2004; 79(12):1495-1500.
202. Culclasure TF, Bray VJ, Hasbargen JA. The significance of hematuria in the anticoagulated patient. *Arch Intern Med*. 1994;154(6):649-652.
203. Van Savage JG, Fried FA. Anticoagulant associated hematuria: a prospective study. *J Urol*. 1995;153(5):1594-1596.
204. Schuster GA, Lewis GA. Clinical significance of hematuria in patients on anticoagulant therapy. *J Urol*. 1987;137(5): 923-925.
205. Avidor Y, Nadu A, Matzkin H. Clinical significance of gross hematuria and its evaluation in patients receiving anticoagulant and aspirin treatment. *Urology*. 2000;55(1): 22-24.

206. Hashash JG, Shamseddeen W, Skoury A, Aoun N, Barada K. Gross lower gastrointestinal bleeding in patients on anticoagulant and/or antiplatelet therapy: endoscopic findings, management, and clinical outcomes. *J Clin Gastroenterol*. 2009;43(1):36-42.
207. Rubin TA, Murdoch M, Nelson DB. Acute GI bleeding in the setting of supratherapeutic international normalized ratio in patients taking warfarin: endoscopic diagnosis, clinical management, and outcomes. *Gastrointest Endosc*. 2003;58(3):369-373.
208. Tang EOY, Lai CS, Lee KK, Wong RS, Cheng G, Chan TY. Relationship between patients' warfarin knowledge and anticoagulation control. *Ann Pharmacother*. 2003;37(1):34-39.
209. Kagansky N, Knobler H, Rimon E, Ozer Z, Levy S. Safety of anticoagulation therapy in well-informed older patients. *Arch Intern Med*. 2004;164(18):2044-2050.
210. Gadisseur APA, Breukink-Engbers WGM, van der Meer FJM, van den Besselaar AMH, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. *Arch Intern Med*. 2003;163(21):2639-2646.
211. Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol*. 2004;126(4):557-564.
212. Laporte S, Quenet S, Buchmüller-Cordier A, et al. Compliance and stability of INR of two oral anticoagulants with different half-lives: a randomised trial. *Thromb Haemost*. 2003;89(3):458-467.
213. Pernod G, Labarère J, Yver J, et al. EDUC'AVK: reduction of oral anticoagulant-related adverse events after patient education: a prospective multicenter open randomized study. *J Gen Intern Med*. 2008;23(9):1441-1446.
214. Machtinger EL, Wang F, Chen LL, Rodriguez M, Wu S, Schillinger D. A visual medication schedule to improve anticoagulation control: a randomized, controlled trial. *Jt Comm J Qual Patient Saf*. 2007;33(10):625-635.
215. Mazor KM, Baril J, Dugan E, Spencer F, Burgwinkle P, Gurwitz JH. Patient education about anticoagulant medication: is narrative evidence or statistical evidence more effective? *Patient Educ Couns*. 2007;69(1-3):145-157.
216. Clark CM, Bayley EW. Evaluation of the use of programmed instruction for patients maintained on warfarin therapy. *Am J Public Health*. 1972;62(8):1135-1139.

Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Table S1—*[Section 2.1] Evidence Profile: Warfarin 10-mg Loading Dose Nomogram Compared With Warfarin 5-mg Loading Dose Nomogram for Warfarin Initiation*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Warfarin 5-mg Loading Dose Nomogram	With Warfarin 10-mg Loading Dose Nomogram	Relative Effect (95% CI)	Risk With Warfarin 5-mg Loading Dose Nomogram	Risk Difference With Warfarin 10-mg Loading Dose Nomogram (95% CI)
Bleeding events (critical outcome)											
420 (3 studies[a-c]), 5-90 d[d]	Serious[e]	No serious inconsistency	Serious[f]	Very serious[g]	Undetected	Very low[e-g] due to risk of bias, indirectness, and imprecision	1/204 (0.49)	2/216 (0.93)[h]	OR 1.90 (0.17-21.1)	Moderate	
										10 per 1,000	9 more per 1,000 (from 8 fewer to 166 more)
Recurrent VTE (critical outcome)											
420 (3 studies[a-c]), 5-90 d	Serious[e]	No serious inconsistency	Serious[f]	Very serious[g]	Undetected	Very low[e-g] due to risk of bias, indirectness, and imprecision	0/204 (0)	3/216 (1.4)[i]	OR 6.72 (0.34-131.88)	Moderate	
										0 per 1,000	…

Bibliography: Crowther MA, Ginsberg J, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med*. 1999;159(1):46-48. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med*. 1997;126:133-136. Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. *Ann Intern Med*. 2003;138:714-419. Quiroz R, Gerhard-Herman M, et al. Comparison of a single end point to determine optimal initial warfarin dosing (5 mg vs 10 mg) for venous thromboembolism. *Am J Cardiol*. 2006;98:535-537. Schulman S, Lockner D, Bergstrom K, Blomback M. Intensive initial oral anticoagulation and shorter heparin treatment in deep vein thrombosis. *Thromb Haemost*. 1984:52:276-280.

[a] All pooled studies included only patients with acute VTE. Studies from which data could be pooled are Kovacs et al, Quiroz et al, and Schulman et al.

[b] Minimal loss to follow-up; adherence to intention-to-treat principle in two of three studies; follow-up period is short but adequate for this outcome; any lack of blinding should not affect objective outcome (laboratory value, international normalized ratio); adequate allocation concealment; and sample size calculations reported for two of three studies.

[c] Results based on only three studies; one study shows no difference; one study shows statistically significant reduction in time to therapeutic international normalized ratio; and one study had two parts to it, with one part showing statistically significant reduction and the other did not.

[d] Five days is the mean follow-up period for patients in the loading dose warfarin group from Schulman et al (this was the shortest period, only mean is available).

[e] Adequate allocation concealment; adjudicators blinded in two of three studies (but caregivers and data collectors blinded in zero of three studies); minimal loss to follow-up; intention to treat followed in two of three studies, but follow-up period is very short in two of three studies (5 d-2 wk).

[f] Indirect given application aimed at VTE outpatients.

[g] No studies were powered to detect differences in bleeding events between groups. Number of events is too sparse to draw any conclusions.

[h] One major bleeding event in the 10-mg group vs none in the 5-mg in Quiroz et al; no bleeding events in either group in Schulman et al; one major bleeding event per group in Kovacs et al.

[i] No recurrent VTE in either group for Quiroz et al or Schulman et al; three in the 10-mg group vs none in the 5-mg group in Kovacs et al.

Table S2—*[Section 2.2] Evidence Profile: Pharmacogenetic-Based Testing vs Usual Dosing Strategies for Patients Initiating Therapy With VKA*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Usual Dosing Strategies	With Pharmacogenetic-Based Testing	Relative Effect (95% CI)	Risk With Usual Dosing strategies	Risk Difference With Pharmacogenetic-Based Testing (95% CI)
Major bleeding (nonfatal) (critical outcome; assessed with clinical evaluation[a])											
468 (3 studies), 1-3 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]	Undetected[c]	Moderate[b,c] due to imprecision	6/234 (2.6)[d]	4/234 (1.7)[e]	OR 0.66 (0.16-2.45)	26 per 1,000[e]	9 fewer per 1,000 (from 21 fewer to 35 more)
Thromboembolism (critical outcome; assessment not reported)											
463 (3 studies), 1-3 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]			2/231 (0.87)[d,f]	0/232 (0)	OR 0 (0-3.4)[f]	9 per 1,000[d,f]	9 fewer per 1,000 (from 9 fewer to 20 more)

Bibliography: Anderson JL, Horne BD, Stevens SM, et al; for Couma-Gen Investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation.* 2007;116(22):2563-2570. Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. *Clin Med Res.* 2005;3(3):137-145. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. *Clin Pharmacol Ther.* 2008;83(3):460-470. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. *Pharmacogenet Genomics.* 2009;19(3):226-234. VKA = vitamin K antagonist.

[a] Bleeding rate in Hillman et al was four of 20, but severity was not reported; included one case hematuria, two cases epistaxis, and one GI bleed in the control group.

[b] Total sample size below optimal information size.

[c] All studies were funded by public or nonprofit organizations.

[d] Control rate is median percentage of events in the usual dosing group across all studies reporting that outcome.

[e] Intervention rate is mean percentage of events across all intervention groups (unweighted).

[f] Hillman et al reported one DVT and one thromboembolism (unclear whether the same or different patients) among 20 control patients and no events in the intervention group. Caraco et al reported no events in both groups. Huang et al reported no VTE in either group. Anderson et al did not separate VTE.

Table S3—*[Section 2.3] Evidence Profile: VKA Started Early vs Late in Heparin Patients With Acute Thromboembolism*

Quality Assessment							Summary of Findings			
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Late	With VKA Started Early	Relative Effect (95% CI)	Risk With Late	Risk Difference With VKA Started Early (95% CI)
Death (critical outcome)											
807 (4 studies), 3-6 mo	No serious risk of bias[a]	Serious[b]	No serious indirectness	Serious[c]	Undetected	Low[a-c] due to inconsistency and imprecision	23/394 (5.8)	27/413 (6.5)	RR 1.28 (0.43-3.85)	58 per 1,000	16 more per 1,000 (from 33 fewer to 166 more)
Recurrent thromboembolism (critical outcome; DVT assessed with venography, Doppler ultrasonography, or impedance plethysmography; PE assessed with lung scanning; left ventricle thrombus assessed with two-dimensional transthoracic echocardiography)											
807 (4 studies), 3-6 mo	Serious[d]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[c,d] due to risk of bias and imprecision	16/394 (4.1)	15/413 (3.6)	RR 0.92 (0.46-1.82)	41 per 1,000	3 fewer per 1,000 (from 22 fewer to 33 more)
Major bleeding (critical outcome; assessed with required blood transfusion or bleeding in body cavity or bleeding that required anticoagulation withdrawal for intracranial or retroperitoneal bleeding or led to hemoglobin level decrease of ≥ 2 g/dL or to death)											
807 (4 studies), 0.5-6 mo	Serious[d]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[c,d] due to risk of bias and imprecision	13/394 (3.3)	16/413 (3.9)	RR 1.22 (0.58-2.56)	33 per 1,000	7 more per 1,000 (from 14 fewer to 51 more)
Hospital utilization (days) (important outcome; better indicated by lower values)											
536 (3 studies), follow-up for hospital, 2 d to 6 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	263	273	...	The mean hospital utilization in the control groups was 14 d	The mean hospital utilization in the intervention groups was 4.07 d lower (4.76-3.37 d lower)

Bibliography: Qayyum F, Holbrook A, Lam J, Kovacs MJ, Schulman S, unpublished data, 2011. PE = pulmonary embolism; RR = risk ratio. See Table S2 legend for expansion of other abbreviation.

[a] For three of four studies, concealment of allocation was unclear. However, this alone was not seen as a compelling reason to downgrade evidence for this outcome. Lack of blinding of health-care professionals in some studies is not likely to affect incidence of this outcome.

[b] The value for the I^2 test for death was 55%; therefore, it was rated down for inconsistency.

[c] The 95% CIs around the absolute risk values were very wide for this outcome.

[d] Potential limitations in design for this outcome, including allocation sequence concealment not reported in three of four studies and health-care professionals blinded in only one study (Hull et al 1990) (outcome assessors were blinded in three of four studies).

Table S4—*[Section 3.1] Evidence Profile: Prolonged INR Recall Intervals Compared With Four-Week Recall Intervals*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With 4-wk Recall Intervals	With Prolonged INR Recall Intervals	Relative Effect (95% CI)	Risk With 4-wk Recall Intervals	Risk Difference With Prolonged INR Recall Intervals (95% CI)
Thromboembolism (critical outcome; assessments variously defined)											
744 (2 studies), 163 patient-y	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[b,c] due to risk of bias and imprecision	5/384 (1.3)	6/360 (1.7)	RR 1.02 (0.13-8.32)	13 per 1,000	0 more per 1,000 (from 11 fewer to 95 more)
Major bleeding (critical outcome; assessments variously defined)											
744 (2 studies), 163 patient-y	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[b,c] due to risk of bias and imprecision	16/384 (4.2)	16/360 (4.4)	RR 1.06 (0.54-2.1)	42 per 1,000	2 more per 1,000 (from 19 fewer to 46 more)

Bibliography: Fihn SD, McDonell MB, Vermes D, et al. A computerized intervention to improve timing of outpatient follow-up: a multicenter randomized trial in patients treated with warfarin. *J Gen Intern Med*. 1994;9:131-139; Pengo V, Barbero F, Biasiolo A, Pegoraro C, Cucchini U, Iliceto S. A comparison between six- and four-week intervals in surveillance of oral anticoagulant treatment. *Am J Clin Pathol*. 2003;120:944-947. INR = international normalized ratio. See Table S3 legend for expansion of other abbreviation.

[a] Time frame is in months.

[b] Lack of blinding; intention to treat not specified in Pengo et al; and adherence to recommended INR recall intervals was not mandated in Fihn et al.

[c] Wide CIs around the estimate of effect.

Table S5—*[Section 3.4] Evidence Profile: Low-Dose Vitamin K Supplementation Compared With Placebo for Patients Taking VKAs To Stabilize INR*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Placebo	With Low-Dose Vitamin K Supplementation	Relative Effect (95% CI)	Risk With Placebo	Risk Difference With Low-Dose Vitamin K Supplementation (95% CI)
Major bleeding (important outcome)											
626 (3 studies), 168-180 d	No serious risk of bias[d]	Serious[b]	No serious indirectness	Serious[c]	Reporting bias strongly suspected[d]	Very low[b-e] due to inconsistency, imprecision, and publication bias	0/219 (0)	3/407 (0.74)	2.61 (0.34-20.28)	0 per 1,000	Not estimable
Thromboembolism (important outcome)											
626 (3 studies), 168-180 d	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Very serious[c]	Reporting bias strongly suspected[d]	See comment	0/219 (0)	0/407 (0)	1.65 (0.08-34.03)	0 per 1,000	Not estimable

Bibliography: Rombouts EK, Rosendaal FR, Van Der Meer FJM. Daily vitamin K supplementation improves anticoagulant stability. *J Thromb Haemost*. 2007;5:2043-2048. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. *Blood*. 2007;109:2419-2423. Gebuis EPA, Rosendaal FR, van Meegen E, van der Meer FJM. Vitamin K1 supplementation to improve the stability of anticoagulation therapy with vitamin K antagonists: a dose-finding study. *Haematologica*. 2011;96(4):583-589.
See Table S2 and S4 legends for expansion of abbreviations.

[a] Time frame is in months.

[b] Full definition of major bleeding not provided in the Sconce et al study. Definition of major bleeding different in each study.

[c] Studies not powered to detect bleeding or thromboembolic events. The sample sizes in trials by both Sconce et al and Rombouts et al were small. The total number of events was extremely low.

[d] Unable to rule out because not enough studies exist to populate funnel plot.

[e] Allocation concealment not reported; uncertain whether outcome adjudicators were blinded.

Table S6—*[Section 3.6] Evidence Profile: Patient Self-Testing/Self-Monitoring Compared With Usual Laboratory-Based Monitoring for VKA Therapy Management*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With vs Usual Laboratory-Based Monitoring	With Patient Self-Testing/Patient Self-Monitoring	Relative Effect (95% CI)	Risk with vs Usual Laboratory-Based Monitoring	Risk Difference With Patient Self-Testing/Patient Self-Monitoring (95% CI)
Thromboembolism (critical outcome; assessed with various methods[b])											
7,759 (14 studies), 4.6-57 mo	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[c] due to risk of bias	149/3,755 (4)	99/4,004 (2.5)	OR 0.58 (0.45-0.75)	40 per 1,000	16 fewer per 1,000 (from 10 fewer to 21 fewer)
Major bleeding (critical outcome; assessed with various definitions[d])											
7,867 (16 studies), 4.6-57 mo	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[c] due to risk of bias	300/3,806 (7.9)	283/4,061 (7)	OR 0.87 (0.75-1.05)	79 per 1,000	10 fewer per 1,000 (from 19 fewer to 4 more)
Mortality (critical outcome; assessed with all-cause mortality)											
6,370 (13 studies), 6-57 mo	Serious[c]	Serious[e]	No serious indirectness	No serious imprecision	Undetected	Low[c,e] due to risk of bias, inconsistency	369/3,123 (11.8)	298/3,247 (9.2)	OR 0.74 (0.63-0.87)	118 per 1,000	28 fewer per 1,000 (from 14 fewer to 40 fewer)[f]

Bibliography: Bloomfield HE, Krause A, Greer N, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med*. 2011;154:472-482. See Table S2 through S4 legends for expansion of abbreviations.

[a] Time frame is in years.

[b] Designated as major by the study or categorized as strokes, new or recurrent symptomatic DVT, PE, or arterial embolism.

[c] Flaws in study design, most commonly an absence of information about the allocation concealment procedure or blinding.

[d] Categorized as major by the study or that met the ISCOAT (Italian Study of Complications of Anticoagulant Therapy) criteria for major bleeding.

[e] Evidence of heterogeneity among studies that was probably attributable to the THINRS (The Home INR Study) Matchar DB, Jacobson A, Dolor R, et al; THINRS Executive Committee and Site Investigators. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med.* 2010;363(17):1608-1620.

[f] The reduction in mortality from all causes was largely influenced by one study.

Table S7—[Section 3.7] Evidence Profile: Dosing Decision Support Compared With Manual Dosing for VKA Therapy

Participants (Studies), Follow-up	Quality Assessment: Risk of Bias	Quality Assessment: Inconsistency	Quality Assessment: Indirectness	Quality Assessment: Imprecision	Quality Assessment: Publication Bias	Quality Assessment: Overall Quality of Evidence	Summary of Findings: Study Event Rates (%): With Manual Dosing	Summary of Findings: Study Event Rates (%): With Dosing Decision Support	Summary of Findings: Relative Effect (95% CI)	Summary of Findings: Anticipated Absolute Effects[a]: Risk With Manual Dosing	Summary of Findings: Anticipated Absolute Effects[a]: Risk Difference With Dosing Decision Support (95% CI)
Thromboembolism—initiation (critical outcome; assessed with: variously defined)											
503 (4 studies), 3 mo	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[b,c] due to risk of bias, imprecision	16/255 (6.3)	9/248 (3.6)	RR 0 (0.27-1.37)	63 per 1,000	63 fewer per 1,000 (from 46 fewer to 23 more)
Major bleeding—initiation (critical outcome; assessment variously defined)											
926 (7 studies[d]), 1-3 mo	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[b,c] due to risk of bias, imprecision	14/473 (3)	5/453 (1.1)	RR 0.43 (0.17-1.09)	30 per 1,000	17 fewer per 1,000 (from 25 fewer to 3 more)
Mortality—initiation (critical outcome; assessed with all-cause mortality)											
748 (5 studies[e]), 1-3 mo	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[b,c] due to risk of bias, imprecision	17/383 (4.4)	12/365 (3.3)	RR 0.73 (0.36-1.46)	44 per 1,000	12 fewer per 1,000 (from 28 fewer to 20 more)
Thromboembolism—maintenance (critical outcome; assessments variously defined)											
14,213 (7 studies[f]), 1-12 mo	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[b] due to risk of bias	122/7,091 (1.7)	109/7,122 (1.5)	RR 0.9 (0.7-1.17)	17 per 1,000	2 fewer per 1,000 (from 5 fewer to 3 more)

(Continued)

Table S7—*Continued*

Participants (Studies), Follow-up	Quality Assessment: Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Summary of Findings: Study Event Rates (%): With Manual Dosing	With Dosing Decision Support	Relative Effect (95% CI)	Anticipated Absolute Effects[a]: Risk With Manual Dosing	Risk Difference With Dosing Decision Support (95% CI)
Major bleeding—maintenance (critical outcome; assessments variously defined)											
14,035 (5 studies[g]), 4.8-12 mo	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[b] due to risk of bias	108/6,999 (1.5)	101/7,036 (1.4)	RR 0.92 (0.71-1.21)	15 per 1,000	1 fewer per 1,000 (from 4 fewer to 3 more)
Mortality—maintenance (critical outcome; assessed with all-cause mortality)											
14,044 (5 studies[h]), 4.8-12 mo	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[b] due to risk of bias	70/6,973 (1)	75/7,071 (1.1)	RR 1.07 (0.78-1.48)	10 per 1,000	1 more per 1,000 (from 2 fewer to 5 more)

Bibliography: Asnis PD, Gardner MJ, Ranawat A, et al. The effectiveness of warfarin dosing from a nomogram compared with house staff dosing. *J Arthroplasty*. 2007;22:213-218. Ageno W, Turpie G. A randomized comparison of a computer-based dosing program with a manual system to monitor oral anticoagulant therapy. *Thromb Res*. 1998;91:237-240. Manotti C, Moia M, Palareti G, et al. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). *Haematologica*. 2001;86:1060-1070. Marco F, Sedano C, Bermudez A, et al. A prospective controlled study of a computer-assisted acenocoumarol dosage program. *Pathophysiol Haemost Thromb*. 2003;33:59-63. Mitra R, Marciello MA, Brain C, Ahangar B, Burke DT. Efficacy of computer-aided dosing of warfarin among patients in a rehabilitation hospital. *Am J Phys Med Rehabil*. 2005;84:423-427. Poller L, Shiach CR, MacCallum PK, et al. Multicentre randomized study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation. *Lancet*. 1998;352:1505-1509. Poller L, Keown M, Ibrahim S, et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs medical staff dosage. *J Thromb Haemost*. 2008;6:935-943. Vadher BD, Patterson DL, Leaning M. Comparison of oral anticoagulant control by a nurse-practitioner using a computer decision-support system with that by clinicians. *Clin Laboratory Haematol*. 1997;19:203-207. Doecke CJ, Cosh DG, Gallus AS. Standardized initial warfarin treatment: evaluation of initial treatment response and maintenance dose prediction by randomized trial, and risk factors for an excessive warfarin response. *Aust N Z J Med*. 1991;21:319-324. Kovacs MJ, Cruickshank M, Wells PS, et al. Randomized assessment of a warfarin nomogram for initial oral anticoagulation after venous thromboembolic disease. *Haemostasis*. 1998;28:62-69. van den Bemt PM, Beinema M, van Roon EN, et al. Initiation of oral anticoagulant therapy in orthopedic and surgical patients: an algorithm compared with routine dosing. *Eur J Clin Pharmacol*. 2002;58:203-208. Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. *Clin Pharm*. 1987;6:37-45.

See Table S2 and S3 legends for expansion of abbreviations.

[a] Time frame is in days to months.

[b] Most studies were unblinded, including patients, health-care providers, and outcome adjudicators.

[c] CI of relative effect encompasses wide range of benefit and harm.

[d] Asnis 2007, Doecke 1991, Kovacs 1998, Landefeld 1992, Vadher 1997 (*BMJ*), van den Bemt 2002, White 1997.

[e] Asnis 2007, Doecke 1991, Kovacs 1998, Landefeld 1992, Vadher 1997 (*BMJ*).

[f] Claes 2005, Fitzmaurice 1996, Fitzmaurice 2000, Mitra 2005, Poller 2008, Vadher 1997, Vadher 1997 (*BMJ*).

[g] Claes 2005, Fitzmaurice 1996, Fitzmaurice 2000, Poller 2008, Vadher 1997.

[h] Claes 2005, Fitzmaurice 1996, Fitzmaurice 2000, Poller 1993, Poller 2008.

Table S8—*[Section 4.1.1] Evidence Profile: Optical Therapeutic INR Range—Higher Target vs 2 to 3*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With INR 2-3	With INR 3-5	Relative Effect (95% CI)	Risk With INR 2-3	Risk Difference With INR 3-5 (95% CI)
Major hemorrhage (critical outcome; assessed per 100 patient-y; various definitions)											
76,646 (17 studies[b])	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low[c,d] due to risk of bias and dose-response gradient	357/59,368 (0.6)	299/17,278 (1.7)	RR 2.7 (1.8-3.9)	6 per 1,000	10 more per 1,000 (from 5 more to 17 more)
Thromboembolism (critical outcome; assessed per 100 patient-y; various definitions)											
835 (10 studies[e])	Serious[f]	Serious[g]	No serious indirectness	No serious imprecision	Undetected	Very low[f,g] due to risk of bias and inconsistency	24/519 (4.6)	15/316 (4.7)	RR 0.9 (0.6-1.3)	Study population	
										46 per 1,000	5 fewer per 1,000 (from 18 fewer to 14 more)
										Moderate	
										50 per 1,000	5 fewer per 1,000 (from 20 fewer to 15 more)

Bibliography: Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ*. 2008;179(3):235-244. See Table S3 and S4 legends for expansion of abbreviations.

[a] Time frame is in months to years.

[b] Six studies had a randomized controlled trial design.

[c] The majority of studies (eight) were retrospective cohorts.

[d] It is biologically plausible that with increased intensity there will be more bleeding.

[e] One study had a randomized controlled design.

[f] Three of four studies had a retrospective cohort design.

[g] Thromboembolic events were more frequent with INR 2 to 3 in two studies, less frequent in one study, and similar in one study.

Table S9—*[Section 4.1.2] Evidence Profile: Optimal Therapeutic INR Range—Lower Target vs 2 to 3*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With INR 2-3	With INR < 2	Relative Effect (95% CI)	Risk With INR 2-3	Risk Difference With INR < 2 (95% CI)
Major hemorrhage (critical outcome; assessed per 100 patient-y; various definitions)											
78,493 (17 studies[b])	Serious[b]	Serious[c]	No serious indirectness	No serious imprecision	Undetected	Very low[b,c] due to risk of bias, inconsistency	357/59,369 (0.6)	123/19,124 (0.6)	RR 1.1 (0.7-1.7)	Study population	
										6 per 1,000	1 more per 1,000 (from 2 fewer to 4 more)
										Moderate	
										23 per 1,000	2 more per 1,000 (from 7 fewer to 16 more)
Thromboembolism (critical outcome; assessed per 100 patient-y)											
827 (4 studies[d])	Serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate[e-g] due to risk of bias, large effect, dose-response gradient	24/520 (4.6)	42/307 (13.7)	RR 3.5 (2.8-4.4)	Study population	
										46 per 1,000	115 more per 1,000 (from 83 more to 157 more)
										Moderate	
										40 per 1,000	100 more per 1,000 (from 72 more to 136 more)

Bibliography: Oakes N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ*. 2008;179(3):235-244. See Table S3 and S4 legends for expansion of abbreviations.

[a] Time frame is in months to years.
[b] Eight of the studies were retrospective cohorts.
[c] Four studies showed higher risk of bleeding with INR < 2.
[d] Only one study had a randomized controlled design.
[e] No explanation was provided.
[f] At least 2.8 times more frequent thromboembolism.
[g] It is biologically plausible with more thromboembolism at lower INR.

Table S10—*[Section 4.2] Evidence Profile: High-Intensity VKA Compared With Moderate-Intensity VKA for Patients With Antiphospholipid Syndrome*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Moderate-Intensity VKA	With High-Intensity VKA	Relative Effect (95% CI)	Risk With Moderate-Intensity VKA	Risk Difference With High-Intensity VKA (95% CI)
Thromboembolism (important outcome; assessed with objective confirmation)											
220 (2 studies[a]), 3 y	Serious[b]	No serious inconsistency	Serious[b]	Serious[c]	Undetected	Very low[b,c] due to risk of bias, indirectness, and imprecision	5/110 (4.5)[a]	11/110 (10)	OR 2.33 (0.82-6.66)	Study population[d]	
										45 per 1,000[3]	54 more per 1,000 (from 8 fewer to 195 more)
										Low[d]	
										50 per 1,000[a]	59 more per 1,000 (from 9 fewer to 210 more)
										High[d]	
										700 per 1,000[a]	145 more per 1,000 (from 43 fewer to 240 more)
Major bleeding (important outcome[e])											
220 (2 studies[e]), 3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[f] due to imprecision	7/110 (6.4)[a]	5/110 (4.5)	OR 0.70 (0.23-2.16)	Study population	
										64 per 1,000[a]	18 fewer per 1,000 (from 48 fewer to 64 more)
										Low	
										25 per 1,000[a]	7 fewer per 1,000 (from 19 fewer to 27 more)
										High	
										100 per 1,000[a]	28 fewer per 1,000 (from 75 fewer to 94 more)

(Continued)

Table S10—*Continued*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Moderate-Intensity VKA	With High-Intensity VKA	Relative Effect (95% CI)	Risk With Moderate-Intensity VKA	Risk Difference With High-Intensity VKA (95% CI)
Mortality (assessed with all-cause mortality)											
220 (2 studies), 3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[f] due to imprecision	2/110 (1.8)	3/110 (2.7)	OR 1.51 (0.3-7.72)	18 per 1,000	9 more per 1,000 (from 13 fewer to 107 more)

Bibliography: Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med*. 2003;349:1133-1138. Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost*. 2005;3:848-853. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. *Am J Med.* 1998:104(4):332-338.
Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med.* 1995;332(15):993-997. See Table S2 legend for expansion of abbreviation.

[a] In the study by Finazzi et al, three patients with nonembolic arterial thrombosis received, as planned, only aspirin. They had no events and have not been included here.

[b] The study by Finazzi et al was open label.

[c] Both studies were designed to show superiority of the more-intensive regimen, not equivalence; 95% CI includes both benefit and significant harm.

[d] Low of 5% from Schulman et al. High of 70% from Khamashta et al.

[e] The types of major hemorrhage were not disclosed.

[f] The 95% CI includes both benefit and significant harm.

Table S11—*[Section 5.0] Evidence Profile: Gradual Withdrawal Compared With Abrupt Withdrawal for Patients Taking VKAs for at Least One Month*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Abrupt Withdrawal	With Gradual Withdrawal	Relative Effect (95% CI)	Risk With Abrupt Withdrawal	Risk Difference With Gradual Withdrawal (95% CI)
Thromboembolism (important outcome; assessed with imaging diagnostics)											
217 (5 studies), 3 mo	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	Undetected	Low[b,c] due to risk of bias, imprecision	14/111 (12.6)[d]	13/106 (12.3)	OR 0.96 (0.42-2.18)	126 per 1,000[d]	4 fewer per 1,000 (from 69 fewer to 113 more)
Mortality (not important outcome; assessed with all-cause mortality)											
217 (5 studies), 1 mo	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	Undetected	Very low[b,c] due to risk of bias, imprecision	1/111 (0.9)	0/106 (0)	OR 0 (0.01-5.6)	9 per 1,000	9 fewer per 1,000 (from 9 fewer to 39 more)d
Major hemorrhage (important outcome)											
217 (5 studies), 1 mo	Serious[b]	No serious inconsistency	No serious indirectness	Very serious[c]	Undetected	Very low[b,c] due to risk of bias, imprecision	1/111 (0.9)	0/106 (0)	OR 1 (0.1-5.6)	9 per 1,000	0 fewer per 1,000 (from 8 fewer to 39 more)[d]

Bibliography: Ascani A, et al. Withdrawal of warfarin after deep vein thrombosis: effects of a low fixed dose on rebound thrombin generation. *Blood Coagul Fibrinolysis*. 1999;10(5):291-295. de Groot MR, et al. Abrupt vs gradual withdrawal of vitamin K antagonist treatment in patients with venous thromboembolic disease: assessment of hypercoagulability and clinical outcome. *Clin Laboratory*. 2000;46(11-12):575-581. Michaels L, Beamish RE. Relapses of thromboembolic disease after discontinued anticoagulant therapy. A comparison of the incidence after abrupt and after gradual termination of treatment. *Am J Cardiol*. 1967;20(5):670-673. Palareti G, et al. Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants–a prospective study. *Thromb Haemost*. 1994;72(2):222-226. Tardy B, et al. Evolution of blood coagulation and fibrinolysis parameters after abrupt vs gradual withdrawal of acenocoumarol in patients with venous thromboembolism: a double-blind randomized study. *Br J Haematol*. 1997;96(1)174-178. See Table S2 legend for expansion of abbreviation.

[a] Time frame is in weeks.

[b] Unclear whether allocation was adequate in Tardy et al, de Groot et al, and Ascani et al. In Michaels and Beamish, it was according to year of birth. Unclear whether allocation was concealed in Tardy, de Groot, and Ascani; not concealed in Michaels and Beamish. Clinicians and patients were not blinded in de Groot, Michaels, Palareti et al, or Ascani.

[c] Very small patient groups and few events.

[d] There is no better source than these trials, so low or high estimates are not provided.

Table S12—*[Section 6.1] Evidence Profile: UFH Weight-Based Nomogram Compared With Fixed Initial Dose for Patients With Thromboembolic Disease*

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Fixed Initial Dose	With Weight-Based Nomogram	Relative Effect (95% CI)	Risk With Fixed Initial Dose	Risk Difference With Weight-Based Nomogram (95% CI)
Thromboembolism (critical outcome)											
292 (3 studies), 2-90 d[b]	Serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	Low[c,d] due to risk of bias and imprecision	8/140 (5.7)[e]	2/152 (1.3)	OR 0.22 (0.02-1.13)[f]	57 per 1,000[e]	44 fewer per 1,000 (from 56 fewer to 7 more)
Major hemorrhage (not important outcome)											
179 (2 studies[g]), 1 wk	Serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	Undetected	Very low[c,d] due to risk of bias and imprecision	1/88 (1.1)	0/91 (0)	OR 0 (0-37.7)[f]	11 per 1,000	11 fewer per 1,000 (from 11 fewer to 291 more)

Bibliography: Becker RC, Ball SP, Eisenberg P, et al; Antithrombotic Therapy Consortium Investigators A randomized, multicenter trial of weight-adjusted intravenous heparin dose titration and point-of-care coagulation monitoring in hospitalized patients with active thromboembolic disease. Am Heart J. 1999:137(1):59-71. Hassan WM, Flaker GC, Feutz C, Petroski GF, Smith, D. Improved anticoagulation with a weight-adjusted heparin nomogram in patients with acute coronary syndromes: a randomized trial. *J Thromb Thrombolysis*. 1995:2(3):245-249. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med.* 1993;119(9):874-881. UFH = unfractionated heparin.

[a] Time frame is in days to weeks.

[b] Only Raschke et al collected data over a 3-mo period.

[c] The studies did not use blinding. Primary outcome was a surrogate marker: time to reach therapeutic or stable therapeutic activated partial thromboplastin time.

[d] None of the studies were powered for clinical outcomes, which were few and poorly reported regarding type and timing.

[e] Two of the eight events occurred after discontinuation of warfarin.

[f] Fisher exact test.

[g] Becker et al reported 2% bleeding without specifying allocation group or type of bleeding.

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Table S13—*[Section 6.2] Evidence Profile: UFH Weight-Adjusted Nonmonitored UFH SC Compared With Weight-Adjusted Nonmonitored LMWH SC for Outpatients With Acute VTE*

	Quality Assessment						Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[a]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Weight-Adjusted Nonmonitored LMWH SC	With Weight-Adjusted Nonmonitored UFH SC	Relative Effect (95% CI)	Risk With Weight-Adjusted Nonmonitored LMWH SC	Risk Difference With Weight-Adjusted Non-monitored UFH SC (95% CI)
Recurrent VTE (critical outcome; assessed objectively with same method as for index event)											
697 (1 study), 3 mo	No serious risk of bias	No serious inconsistency	Serious[b]	Serious[c]	Undetected	Low[b,c] due to indirectness and imprecision	12/352 (3.4)	13/345 (3.8)	OR 1.11 (0.49-2.52)	34 per 1,000	4 more per 1,000 (from 17 fewer to 48 more)
Major bleeding (critical outcome; assessed with ISTH criteria)											
697 (1 study), 3 mo	No serious risk of bias	No serious inconsistency	Serious[b]	Serious[c]	Undetected	Low[b,c] due to indirectness and imprecision	12/352 (3.4)	6/345 (1.7)	OR 0.5 (0.17-1.34)	34 per 1,000	17 fewer per 1,000 (from 28 fewer to 11 more)
Mortality (not important outcome)											
697 (1 study), 3 mo	No serious risk of bias	No serious inconsistency	Serious[b]	Serious[c]	Undetected	Low[b,c] due to indirectness and imprecision	22/352 (6.3)	18/345 (5.2)	OR 0.83 (0.43-1.57)	62 per 1,000	10 fewer per 1,000 (from 35 fewer to 32 more)

Bibliography: Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006;296:935-942. LMWH = low-molecular-weight heparin; SC = subcutaneous. See Table S12 legend for expansion of other abbreviation.

[a] Time frame is in weeks.

[b] The comparison should actually be vs fixed-dose UFH SC with monitoring, but weight-adjusted UFH SC has only been compared directly with weight-adjusted LMWH. Thus, the comparison is indirect.

[c] Due to premature discontinuation, the study was not powered to demonstrate equivalence.

Table S14—*[Section 9.1] Evidence Profile: Vitamin K vs Only Withholding VKA for Patients on Warfarin With Elevated INR (4.5-10) Without Evidence of Bleeding*[a]

Quality Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects[b]	
Participants (Studies), Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Only Holding VKA	With Vitamin K	Relative Effect (95% CI)	Risk With Only Holding VKA	Risk Difference With Vitamin K (95% CI)
Major bleeding (critical outcome)											
923 (4 studies[c]), 1-3 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[e,f] due to imprecision	4/471 (0.8)	10/452 (2.2)	OR 2.6 (0.8-9.8)	8 per 1,000	13 more per 1,000 (from 2 fewer to 69 more)
Thromboembolism (important outcome)											
864 (3 studies[g]), 1-3 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[e,f] due to imprecision	4/441 (0.91)	5/423 (1.2)	OR 1.3 (0.3-6.6)	9 per 1,000	3 more per 1,000 (from 6 fewer to 48 more)
Mortality (not important outcome; assessed with all-cause mortality)											
863 (3 studies[g]), 1-3 mo[d]	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious[f]	Undetected	Moderate[e,f] due to imprecision	13/441 (2.9)	16/422 (3.8)	OR 1.3 (0.6-2.9)	29 per 1,000	9 more per 1,000 (from 12 fewer to 51 more)

Bibliography: Crowther MA, Ageno W, Garcia D, et al. Oral vitamin K vs placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. *Ann Intern Med*. 2009;150(5):293-300. Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomized controlled trial. *Lancet*. 2000;356:1551-1553. Ageno W, Crowther M, Steidl L, et al. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a randomized controlled trial. *J Thromb Haemostasis*. 2002;88:48-51. Ageno W, Garcia D, Silingardi M, Galli M, Crowther M. A randomized trial comparing 1 mg of oral vitamin K with no treatment in the management of warfarin-associated coagulopathy in patients with mechanical heart valves. *J Am Coll Cardiol*. 2005;46(4): 730-742. See Table S2 and S4 for expansion of abbreviations.

[a] INR 6.0-12.0 in Ageno et al 2005.
[b] Time frame is in days.
[c] None of the studies specified whether any bleeding events were fatal or intracranial.
[d] Follow-up was 3 mo in both studies by Crowther et al.
[e] Two small studies, Ageno 2002 and Ageno 2005, were open label.
[f] Wide CIs encompassing both benefit and significant harm.
[g] Ageno et al 2005 did not report thromboembolism, and Ageno et al 2002 did not report deaths.